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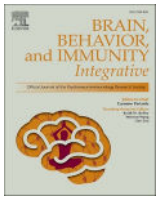

Lifestyle medicine for healthy cognitive aging: A narrative review

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ABSTRACT

Many countries across the globe are experiencing aging populations, which brings into question the fitness and capacity of these populations. Rates of neurodegenerative diseases worldwide are increasing, even after adjusting for increasing lifespans. This worrying trend motivates taking steps in the population to prevent dementia. This review summarizes the work on lifestyle medicine based prevention of dementia and cognitive decline using multiple modalities and interventions. Our results bring hope to those seeking to stay cognitively healthy in advanced age through combinations of diet, exercise, and mindfulness based interventions. Leveraging cheap and scalable interventions is an important strategy for alleviating the expected tide of neurodegenerative illnesses. This review covers the potential lifestyle and dietary interventions which can alleviate Alzheimer's disease burden, paving the way for population level preventative approaches for neurodegenerative disease.

1. Introduction

Neurodegenerative diseases and dementias significantly raise healthcare spending, and present significant challenges for caregivers. Care of dementia patients presents distinct challenges from other forms of care, causing significant strain on families (Smith et al., 2022) and paid caregivers (Greenwood et al., 2018; Posner et al., 2015). Older people with dementia are also more vulnerable to abuse (Fang and Yan, 2018), and less capable of self-sufficiency (Cipriani et al., 2012), and are perceived in a lower light by others (Klůzová Kráčmarová et al., 2022), contributing to a decreased well-being and self-esteem (dos Santos et al., 2018).

Western nations face lopsided age pyramids which make funding retirement challenging in the future (Bonoli and Shinkawa, 2006). Social Security funds in the US are expected to dwindle to zero by 2033 unless changes are made to funding, which will require some combination of cutting benefits, increasing funding, or increasing the retirement age (CBO's, 2022). Similar problems exist among European Union (EU) member nations (Heer et al., 2023).

The issue of an aging population is worsened by the increased care costs associated with elder care. This issue motivates the study of interventions that can improve cognitive health in later life and maintain healthy independence in the aged population.

Age-associated cognitive decline exacts a massive toll on societies. The median survival from dementia onset to death is 5.0 years, compared to 9.6 years for age-matched controls (Joling et al., 2020). People experiencing dementia are institutionalized after 3.9 years after diagnosis (median value), leaving approximately 1.1 years of institutionalization before death (Joling et al., 2020). Dementia severity is strongly inversely correlated with quality of life (Castro-Monteiro et al., 2016). Institutionalization is very costly, and consumes a considerable amount of resources. Also, the quality of life for caregivers is inversely correlated with the extent of neuropsychiatric symptoms (Takai et al., 2011; Andrén and Elmståhl, 2007). Women are twice as likely to be the family caregiver for an adult with dementia as men (Andrén and Elmståhl, 2007), and caregiver burden can be a significant retarding factor in the upward mobility of low-income families (Martinez-Martin et al., 2019).

Dementia was estimated to cost $604 billion worldwide, in 2010, with 70 % of the costs born by western Europe and North America (Wimo et al., 2013). It is estimated that the care need (for all conditions) will comprise one-fifth to two-fifths of the work time of the entire paid labour force; if compensated, this would amount to between 16 and 32 percent of gross domestic product (GDP) (King et al., 2021).

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The Covid-19 pandemic may also have an influence on neurodegenerative disease rates. SARS-CoV-2 has been hypothesized to cause pathological brain changes, due to the ability of viral proteins to disrupt the blood brain barrier (Song et al., 2023). Alzheimer's has been associated with COVID-19 disease in seniors (Wang et al., 2022), and memory problems are a common post Covid-19 symptom (Ahmed et al., 2022; Ding and Zhao, 2023).

It is proposed that the spike protein of SARS-CoV-2 has amyloidogenic potential (Seneff et al., 2022), which is supported by computational prediction (Tetz and Tetz, 2022), and one study showing aggregation *in vitro* by SARS-CoV-2 spike protein (S) peptides (Nyström and Hammarström, 2022). Spike is also hypothesized to interact with other proteins to form aggregates (Liu et al., 2021; Idrees and Kumar, 2021), and modified SARS-CoV spike protein can oligomerize with other copies of itself (Song et al., 2004). Spike protein itself is capable of crossing the blood brain barrier, and is hypothesized to function as an amyloidogenic seed (Nyström and Hammarström, 2022; Oldfield et al., 2021; Seneff et al., n.d), and cases have emerged of cognitive impairment after infection (Dubey et al., 2023) or vaccination (which also produces SARS-CoV-2 spike protein) (Chakrabarti et al., 2022).

2. Dementia onset

2.1. Biological mechanism

In Alzheimer's disease the development of amyloid plaques and neurofibrillary tangles seems to be the primary causes of the loss of neurons' ability to function. The amyloid plaques are extracellular formations consisting in an aggregation of amyloid-β peptides while neurofibrillary tangles are fibrillary structures in neurons formed by an aggregation of protein Tau (Stefanoska et al., n.d). These two types of aggregations have been the primary targets for defining a potential treatment for Alzheimer's since the disease was first examined. In recent years, special attention has been placed on the study of β-amyloids plaques and how to prevent them, unfortunately without great success, as a result, the focus has also shifted to the investigation of the role played by protein tau in the progression of this disease (Zhang et al., 2022). Several research are currently being conducted to learn how to stop or slow down the growth of these agglomerations, and the study for this thesis is founded directly on this concept.

AD is a non-reversible type of dementia whose symptoms include numerous disturbances of mental functions, such as the use of language, perception, memory disfunction as well as cognitive skills. It is characterized by the presence of extracellular amyloid plaques and intracellular neurofibrillary tangles within the afflicted brain (Hampel et al., 2021).

One of the main hypotheses behind the development of AD is the amyloid cascade hypothesis, based on the idea that Aβ monomers tend to aggregate into oligomers and fibrils leading to neurotoxicity and dementia. Aβ monomers can be classified in two main forms composed respectively by 40 ($A\beta_{1-40}$) and 42 residues ($A\beta_{1-42}$): the latter being the most cytotoxic (Findeis, 2007).

2.1.1. Amyloid cascade hypothesis: aggregation process

The progression from amyloid to clinical manifestations can often take longer than one decade (Davies et al., 1988). During this time, aggregation is progressing.

Once amyloid beta monomer is released in the synaptic cleft, it starts to associate into various types of structures including oligomers, protofibrils, amyloid fibrils and amorphous aggregates. Oligomers have revealed to be the most neurotoxic species in AD (Diociaiuti et al., 2014), in fact being soluble they are able to spread into the brain (Walsh and Selkoe, 2004); although, fibrils are larger, insoluble and can further assemble into amyloid plaques which will deposit in the intracellular environment blocking neural communication (Stromer and Serpell, 2005).

2.1.2. The role of protein Tau

A group of neurodegenerative disorders known as tauopathies are characterized by an abnormal concentration of phosphorylated tau protein in the human brain. Many clinicopathological disorders, including Alzheimer's disease, have been linked to tauopathy. A series of post-translational changes that can be applied to tau can reduce the protein's structure, function, turnover, or even cause multimeric aggregation. These alterations also include acetylation, methylation, nitration, glycosylation, and sumoylation in addition to phosphorylation (Muralidar et al., 2020). Because post-translational phosphorylation is regarded as a defining feature of all tauopathies, it is still the change of tau that has been the subject of most of the research.

One of the main factors contributing to the development of Alzheimer's disease has been identified as the protein Tau, specifically its hyperphosphorylation. Protein Tau is an intrinsically disordered protein that, by its direct interaction with tubulin dimers, is most strongly linked to the stabilization of cytoskeletal and mitotic microtubules (MTs).

The cytoskeleton of the cell, which is made up primarily of microtubules and is crucial for intracellular movement, signaling, and cell division, is a structural component of the cell. Each tubulin protein consists of a well-defined globular domain (core) and a disorganized, negatively charged C-terminal tail (CTT), which is a target for numerous post-translational changes (PTMs) (Marien et al., 2023). Tau plays a crucial role in controlling axon outgrowth and preserving the integrity and trafficking of axonal cytoskeleton (Giovinazzo et al., 2021). For a long time, it was believed that Tau's only job was to keep MTs stable. Therefore, more recently, the emphasis has switched to its capacities to regulate the MTs dynamics rather than stabilize them (Limorenko and Lashuel, 2022).

In healthy brains, protein Tau is bound to microtubules and has a specific amount of phosphate molecules attached to it; however, in AD brains, this system is altered, resulting in an unnatural increase in the phosphorylation. Altered protein Tau have a propensity to organize into paired helical filaments, which then congregate into intractable neurofibrillary tangles. This aggregation causes neurotoxicity by altering the cytoskeletal architecture, axonal transport, and mitochondrial respiration, among other ways. Transport of nutrients and other crucial chemicals inside neurons is inhibited by tau tangles. When the disease advances, they spread throughout the brain like plaques, starting close to the entorhinal cortex, moving to the hippocampus, and eventually covering the cerebral cortex (Ricci et al., 2021). Although research indicates that the tau protein plays a crucial part in the progression of Alzheimer's disease, which makes it an ideal candidate to discovery and development a drug to slow the disease's progression, the molecular and cellular mechanisms that triggers tau protein misfolding and aggregation and promote the development of tauopathies in the brain are still unknown.

2.2. Factors impacting onset

Age-normalized rates of dementia control for the expected increase in dementia diagnoses with age, and rates of dementia have declined in recent years (Farina et al., 2022). Approximately half of this decline in dementia prevalence can be attributed to greater levels of education in later-born cohorts. While this represents positive news, dementia remains a debilitating diagnosis.

In addition to education level, sex is a factor in dementia prevalence, with women more likely to experience dementia than men (Hudomiet et al., 2022), and people with lower incomes are more likely to experience dementia (age-adjusted). Some differences exist in race-stratified rates of dementia, where dementia is more prevalent in Blacks and Hispanics when compared to Whites when ages are normalized (Hudomiet et al., 2022).

A recent review has provided a graphic illustration of modifiable risk factors for cognitive decline (Fig. 1 (Baumgart et al., 2015)). Strong evidence exists for the association of traumatic brain injury, obesity,

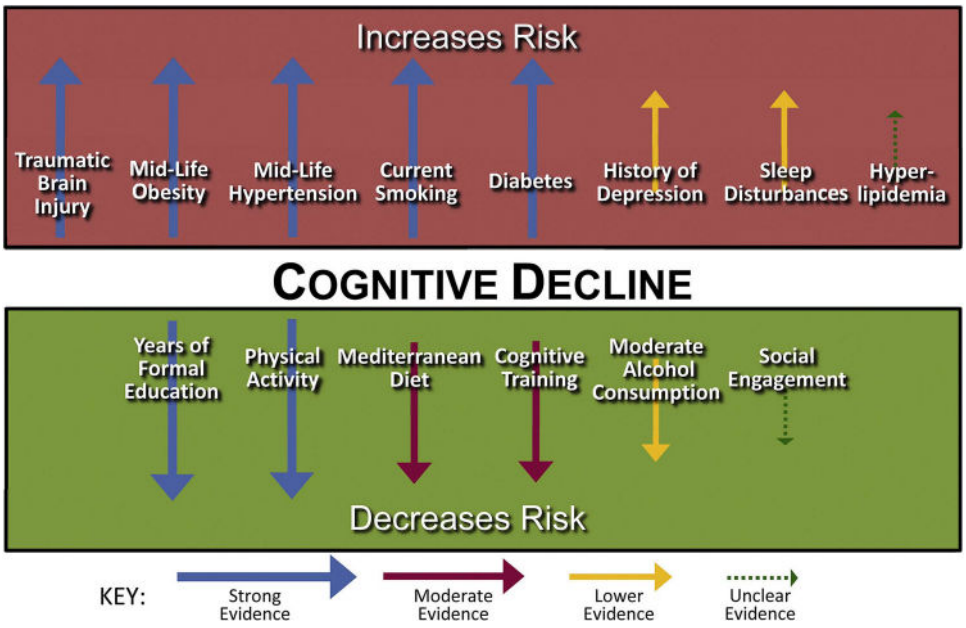

Fig. 1. Modifiable lifestyle factors and risk of age-related cognitive decline. Upward pointing arrows denote factors which increase risk of dementia and downward pointing arrows denote factors which lower risk of dementia. Arrow color denotes level of evidence. Blue, strong evidence; red, moderate evidence; yellow, lower evidence; dotted green, unclear evidence. Reproduced from (Baumgart et al., 2015) under a CC BY-NC-ND 4.0 DEED license.

hypertension, smoking, and diabetes with cognitive decline. Strong evidence exists for the protective effects of education and physical activity on cognitive decline, while moderate quality evidence exists for the protective impacts of a Mediterranean diet and cognitive training against age-related cognitive decline (Baumgart et al., 2015). Lower quality evidence exists for the positive association of depression and sleep disturbances with age-related cognitive decline and the negative (i.e. protective) association of moderate alcohol consumption against cognitive decline.

2.3. Biomarkers for dementia

Given the long time duration of dementia onset, which can occur over decades (Davies et al., 1988), significant attention has been given to the possibility of predicting dementia. The most significant predictive factors for dementia risk are high age, low education, hypertension, hypercholesterolaemia and obesity (Kivipelto et al., 2006). The cardiovascular risk factors, aging and dementia (CAIDE) study developed a useful predictive model, which takes into account age, education, hypertension, obesity and hyperlipidemia, which is capable of predicting dementia risk four decades after the assessment (Exalto et al., 2014). Other biomarkers may be combined with this composite score for greater predictability.

A short cognitive test, combined with plasma P-tau, plasma Aβ42/Aβ40, plasma neurofilament light, APOE genotype, and an Alzheimer's disease specific magnetic resonance imaging (MRI) measure can accurately predict conversion to Alzheimer's disease (Palmqvist et al., 2021). This is considered over the shorter term, and the tool was used to predict conversion to AD within 4 years. It is available as a web tool that only requires age, education, performance on three cognitive tests, one's APOE4 allele status and plasma P-tau (http://predictAD.app).

A recent study published in JAMA Neurology demonstrated that a commercially available plasma p-tau217 immunoassay accurately detects biological Alzheimer's disease (AD), comparable to results obtained using cerebrospinal fluid (CSF) biomarkers (Ashton et al., 2024). The study highlights the reproducibility of cut-offs across different cohorts and the assay's ability to detect longitudinal changes, even in the preclinical stage of AD (Ashton et al., 2024).

The plasma p-tau217 immunoassay utilized in the study is now commercially available through AlzPath (https://alzpath.bio/patients/). This simple blood test exhibits up to 96 % accuracy in identifying elevated levels of beta amyloid and up to 97 % accuracy in identifying tau (Ashton et al., 2024). These findings represent a significant advancement in the diagnosis and monitoring of Alzheimer's disease.

Further insights reveal the presence of pT217-tau in its earliest form within neurons during the early stages of degeneration (Datta et al., 2024). Additionally, evidence suggests the "seeding" of pT217-tau between neurons, shedding light on the pathophysiological mechanisms underlying Alzheimer's disease progression (Datta et al., 2024). The plasma p-tau217 immunoassay is a valuable tool for early detection, disease monitoring, and advancing our understanding of Alzheimer's disease pathology.

3. Interventions

3.1. Metabolic interventions

Aging decreases resting metabolic rate (RMR), which is partially attributable to losses in fat-free mass (FFM, i.e. muscle and bone), though there is a decline independent of FFM (Poehlman et al., 1994). Additionally central adiposity increases as one ages (Palmer and Jensen, 2022), and metabolic changes occur regularly, leading experts to classify metabolic dysregulation as hallmarks of aging (López-Otín et al., 2013). Excess body fat can also alter hormone balance, as adipose tissue can promote estrogen production (Nelson and Bulun, 2001).

There is also significant crosstalk between metabolic health and brain health, where metabolically unhealthy individual have lower brain volumes into old age than their metabolically fit counterparts (Angoff et al., 2022).

3.1.1. Dietary factors

When it comes to healthy aging, it is important to avoid insulin resistance, as this is a significant predictor of age-related disease (Facchini et al., 2001). Those who live to ages past 100 (centenarians) have better insulin sensitivity than their counterparts who die at younger ages (Paolisso et al., 1996). One of the most robust findings in the field of gerontology research is the relationship between calorie restriction and longevity (Mitchell et al., 2016). Famously, the Okinawans, who are

renowned for their high proportion of centenarians, eat only 83 % the number of calories as their counterparts in mainland Japan (Willcox et al., 2007). Time restricted eating has been shown to improve beta-amyloid clearance in a mouse model (Whittaker et al., 2023), and this may be helpful for prevention of dementia in humans, though this relationship requires greater study to translate animal models into clinical recommendations.

Adherence to a Mediterranean diet is associated with a lower level of cognitive decline in older individuals (Dominguez et al., 2021). A specialized diet designed to reduce the incidence of dementia, named the MedDiet-DASH Intervention for Neurodegenerative Delay (MIND) diet, reduces the incidence of cognitive dysfunction (Morris et al., 2015), it's composition is a modified Mediterranean diet, emphasizing the consumption of green leafy vegetables and berries (Morris et al., 2015).

Specific nutrients may be preventative of dementia. Vitamin D (Russ et al., 2016; Shea et al., 2023) and magnesium (Tao et al., 2022) may be helpful in the prevention of dementia. For magnesium, the bioavailable forms of magnesium taurate and magnesium L-threonate increase magnesium levels in brain cells; hence they may be useful in the treatment of depression and Alzheimer's disease (Uysal et al., 2019; Li et al., 2014).

Resveratrol supplementation delays the progression of cognitive impairment relative to the placebo group (Tosatti et al., 2022; Buglio et al., 2022). Other over-the-counter (OTC) available supplements have been examined for their impact on AD in a 2018 review (Butler et al., 2018). The meta-analysis examined omega-3 fatty acids, soy, gingko biloba, B vitamins, vitamin D, vitamin C and several multivitamins, concluding that there was currently no high quality evidence for the effect of any OTC interventions on dementia; besides a positive impact of Vitamin B12 with folic acid on memory performance (Walker et al., 2012).

Berries have been studied for their impact on cognition, and berry extracts may be associated with greater performance on memory tasks (Whyte et al., 2018). Daily cocoa consumption was not associated with cognitive performance, although multivitamin supplements were (Baker et al., 2023).

Table 1 below has been adapted from (Dominguez and Barbagallo, 2018; Gregory et al., 2021; Chang et al., 2016) and shows the evidentiary basis underlying several nutraceuticals for preventing or treating dementia.

3.1.2. Exercise

Exercise has benefits to the brain and is a promising non-pharmacological therapy for cognitive dysfunction (Lu et al., 2023). Numerous randomized controlled trials (RCTs) have reported the positive effects of exercise on cognitive function, ADLs, and neuropsychiatric symptoms in patients with cognitive impairment (Mollinedo Cardalda et al., 2019; Bolandzadeh et al., 2015). Neuroimaging studies also have shown that exercise is beneficial in enhancing functional brain plasticity (Ji et al., 2021).

Exercise may exert protective effects on cognitive function by: 1) raising the levels of growth factors such as brain-derived neurotrophic factor (BDNF) and insulin-like growth factor (IGF-1), 2) regulating neuroinflammation, 3) relieving oxidative stress, 4) increasing cerebral blood flow, 5) reducing Aβ concentration and inhibiting tau phosphorylation, 6) boosting hippocampal neurogenesis, 7) reducing neurovascular disease, and 8) upregulateing autophagy (Zhao, 2024).

High-intensity interval training (HIIT) is recommended a minimum of twice per week for those capable of performing HIIT. For those who cannot do HIT, movement and walking are recommended. A study published in the Journal of Epidemiology and Community Health found that adults who incorporated a few minutes of vigorous activity into their daily routines saw improvements in memory, planning and organizational skills (Mitchell et al., 2023).

A recent study used a network meta-analysis and compared the relative efficacy of various types of exercise interventions in global

Table 1
Nutritional factors and their impacts on dementia. Interventions are grouped into sections, judging by the level of evidence justifying their use in dementia: 'Evidence for efficacy in dementia treatment', 'Limited evidence for efficacy in dementia', 'Unlikely to have a positive impact on dementia'.

Intervention	Effect
Evidence for efficacy in dementia prevention or treatment	
Magnesium	Low serum magnesium levels associated with a 32 % [95 % CI: 2 %, 69 %] increase in dementia risk. High serum magnesium levels associated with a 30 % [95 % CI: 2 %, 67 %] increase in dementia risk (Kieboom et al., 2017).
Cocoa	Improved cerebral blood flow (Lamport et al., 2015), chocolate consumption associated with 41 % [95 % CI: 8 %, 62 %] lower risk of cognitive decline (Moreira et al., 2016)
Saffron	In mild to moderate AD, the experimental group given saffron performed better on cognitive tests (Akhondzadeh et al., 2010a) Comparable to memantine (Farokhnia et al., 2014) and donepezil (Akhondzadeh et al., 2010b)(pharmaceutical products) in reducing cognitive decline
Vitamin A	Beneficial effect long term (>18 years) but not short term (Grodstein et al., 2007)
Chinese herbal medicine and pharmacotherapy	Improved cognitive function (Sawangjit et al., 2023)
Vinpocetine	Improved cognitive function (Sawangjit et al., 2023)
Huperzia serrata	Improvement in activities of daily living score (Sawangjit et al., 2023)
Ashwaganda	Significant improvement in memory and cognitive function (Choudhary et al., 2017)
Bacopa monnieri	Improvement in cognitive function when combined with astaxanthin, phosphatidylserine, and vitamin E for subjects with MCI (Zanotta et al., 2014)
Gotu Kola	Improvement in working memory (Fitriana et al., 2021)
Lion's Mane	Improvement in cognitive tests in 71 % of patients taking Lion's Mane vs. improvement in 7 % of patients in placebo group (Mori et al., 2009). Improvement in activities of daily living for patients with mild AD (Li et al., 2020)
Resveratrol	Delays the progression of cognitive impairment relative to the placebo group (Tosatti et al., 2022; Buglio et al., 2022).
Limited evidence for efficacy in dementia	
Gingko Biloba	Did not reduce cognitive decline (Snitz et al., 2009) Modest improvement in cognitive function in AD subjects (Hashiguchi et al., 2015; Janssen et al., 2010; Yuan et al., 2017) Improvement in Activities of Daily Living (ADLs) for AD patients (Canevelli et al., 2014; Liu et al., 2019)
Caffeine	May reduce levels of cognitive decline (Chen et al., 2020)
(-)-Epigallocatechin−3-gallate (EGCG)	Inconsistent evidence (Song et al., 2012)
Soy isoflavones	Nonsignificant trend towards cognitive improvement (Henderson et al., 2012) Short term improvements which reverse longer term (Soni et al., 2014)
Ginseng	Nonsignificant short-term improvements in cognitive function in AD patients (Lee et al., 2008)
Photobiomodulation	Preliminary positive results (Salehpour et al., 2021) Nonsignificant improvements (Stephan et al., 2022) Nonsignificant effects in short duration trial (Berman et al., n.d)
Unlikely to have a positive impact on dementia	
Omega 3 fatty acids	Non-significant effects (Dominguez and Barbagallo, 2018)

(continued on next page)

Table 1 (*continued*)

Intervention	Effect
Curcumin	Non-significant effects (Dominguez and Barbagallo, 2018)

cognition, executive function, and memory function in patients with cognitive impairment of MCI or dementia (Huang et al., 2022). The meta-analysis was based on 73 articles from 71 studies and included 5606 participants. This study suggests that resistance exercise has the highest probability of being the most effective exercise type for slowing cognitive decline among patients with cognitive impairment, especially for patients with dementia.

Those concerned can begin by moving more throughout the day and avoiding sitting for extended periods. Incorporating a daily walk, preferably outdoors, and working up to a minimum of 30 minutes can be a healthy habit. A study published in JAMA Neurology found that as little as 3800 steps a day reduced the risk of dementia by 25 % (del Pozo Cruz et al., 2022).

Among endurance trained individuals, age-related declines in mitochondrial oxidative capacity were not observed (Lanza et al., 2008). Endurance exercise also prevents cognitive decline in older adults (Muscari et al., 2010). Low aerobic fitness is associated with a much higher degree of mild cognitive impairment (OR=4.5), and a ten to fourteen times greater risk of AD for those who could not meet the performance threshold in the two minute step test (Plácido et al., 2019).

3.1.3. Sleep

Mechanistically, sleep is important as it allows the brain to remove amyloid-β deposits via the glymphatic system (Vaou et al., 2018; Xie et al., 2013). A vicious cycle can manifest, as Alzheimer's disease (AD) can negatively impact sleep, thereby accelerating the progression of AD (West et al., 2017). Even before cognitive decline, sleep problems can manifest (Wang and Holtzman, 2020; Ju et al., 2014), and 25–66 % of AD patients exhibit sleep disturbances (Bianchetti et al., 1995; Guarnieri et al., 2012).

Sleep duration of 6 hours or less at age 50, 60 or 70 is associated with a 30 % increased risk of dementia (Sabia et al., 2021). Prolonged sleep duration(>9 hours) is also associated with an increased (doubled) risk of dementia (Westwood et al., 2017).

3.2. Mental stimulation

One of the most feared outcomes of aging is a loss of cognition. Many elderly people do suffer from dementia, whether in mild or severe forms. Learning into adulthood is important to maintain cognitive health (Antoniou and Wright, 2017; Hughes, 2010). Lifelong learning is practiced by a subset of the population, and the European Commission set a goal for 15 % of adults aged 25–64 should participate in lifelong learning, implying that the actual rate was lower than that (Beblavy et al., 2014). Lower levels of education are associated with the development of dementia (Ma'u et al., 2021), and everyday intellectual engagement is protective against cognitive decline (Staff et al., 2018; Bransby et al., 2022).

Older adults may feel out of place in some educational settings, such as university, where the student body is often much younger. People also have conceptions about what the typical learner should look like, which can be a barrier to adult education.

The impacts of adult education on cognitive health have been studied, finding a positive association. In a 2021 survey 17.9 % of USA citizens over the age of 15 read every day, compared to 20.7 % in 2012 (Time Spent Reading in the US, 2023). In a recent study of people advanced in age; regular cognitive activities, including book reading, were associated with lower odds of mild cognitive impairment (MCI) (Geda et al., 2011; Hughes et al., 2010; Wu et al., 2023). MCI often precedes the development of dementia (Knopman and Petersen, 2014), and those with MCI develop dementia at rates of 10–15 % (Petersen et al., 2001).

Years of education correlates with lower dementia risk. Relative to those with 5 years or less of formal education, those with 6–8 years of education had a 43 % reduced risk of dementia, and those with 9 or more years of education had an 84 % reduced risk of dementia (Ngandu et al., 2007). While years of education is an imperfect proxy for learning, and there are other mediating factors, interventional studies show promise. A care home study where participants were assigned to reading groups showed significant improvements in patient Neuropsychiatric Inventory Questionnaire (NPI-Q) score (Billington et al., 2013).

Hobbies, including engagement with music (Fang et al., 2017), are associated with lower rates of cognitive decline and dementia (Matsumura et al., 2023; Sommerlad et al., 2020; Kim et al., 2020).

3.3. Pharmaceutical interventions

Several investigational and approved drugs exist to putatively treat Alzheimer's disease, with differing levels of treatment efficacy and toxicity. These compounds act on several mechanisms. The first class are the acetylcholinesterase inhibitors: physostigmine (Bentley et al., 2008), tacrine (Chatellier and Lacomblez, 1990), velnacrine (Zemlan, 1996), metrifonate (Cummings et al., 1998), rivastigmine, Donepezil and Galantamine (Nordberg et al., 2009). Other classes include the antagonists of NMDA receptors, which contains memantine (Reisberg et al., 2003); the inhibitors of beta-secretase, sargramostim (Potter et al., 2021) and rosiglitazone (Gold et al., 2010); the anti-tau drug ABBV-8E12 (West et al., 2017), and other drugs (Bateman et al., 2017) and vaccines in development t (Plascencia-Villa and Perry, 2023).

Treatments targeting the behavioural manifestations of Alzheimer's include circadin (Wade et al., 2014), AVP-923 (Cummings et al., 2015) and the antipsychotic primavenserin (Gold et al., 2010). Alzheimer's medications remain investigational with limited long-term evidence of efficacy.

4. Outlook and conclusion

While aging is inevitable, the development of dementia can be reduced through lifestyle and dietary interventions. Several accessible interventions show robust evidence for a preventative effect on Alzheimer's disease development and form a coherent strategy for aging individuals to maintain cognitive function and independence as they age.

A large aging population presents a significant need for the prevention of Alzheimer's. Given the multi-year progression of cognitive impairment to dementia (Thaipisuttikul et al., 2022), it is important to begin preventative efforts early. These interventions aim to retain the independence and autonomy of the elders within a society. Not only are their individual lives important, but interactions with elders also positively benefit younger generations who may learn from them (Streetman et al., 1999).

CRediT authorship contribution statement

Jack Tuszynski: Writing – review & editing, Writing – original draft, Investigation. **Suzanne Gazda:** Writing – original draft, Investigation. **Paul Marik:** Writing – review & editing, Writing – original draft, Investigation, Conceptualization. **Matthew Halma:** Writing – review & editing, Writing – original draft, Supervision, Project administration, Investigation, Conceptualization.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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