



Modifiable Risk Factors for Alzheimer's Disease

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Since first described in the early 1900s, Alzheimer's disease (AD) has risen exponentially in prevalence and concern. Research still drives to understand the etiology and pathogenesis of this disease and what risk factors can attribute to AD. With a majority of AD cases being of sporadic origin, the increasing exponential growth of an aged population and a lack of treatment, it is imperative to discover an easy accessible preventative method for AD. Some risk factors can increase the propensity of AD such as aging, sex, and genetics. Moreover, there are also modifiable risk factors—in terms of treatable medical conditions and lifestyle choices—that play a role in developing AD. These risk factors have their own biological mechanisms that may contribute to AD etiology and pathological consequences. In this review article, we will discuss modifiable risk factors and discuss the current literature of how each of these factors interplay into AD development and progression and if strategically analyzed and treated, could aid in protection against this neurodegenerative disease.

Keywords: Alzheimer's disease, risk factors, comorbidities, vascular disease, traumatic brain injury, epilepsy, depression, lifestyle

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INTRODUCTION

Alzheimer's dementia is an age-related neurodegenerative disease characterized by several neuropathological markers including extracellular amyloid- β (A β) plaques, intracellular neurofibrillary tangles (NFTs), inflammation, synaptic impairment, and neuronal loss that leads to cognitive impairment (Querfurth and LaFerla, 2010). A multitude of studies has shown strong evidence for the concept that the misfolding, aggregation and brain accumulation of protein aggregates are a triggering event in the pathogenesis of Alzheimer's disease (AD) and responsible for the subsequent pathological alterations that lead to the clinical disease (Moreno-Gonzalez and Soto, 2011). Due to the progressive aging of the population, the number of people affected by AD in the United States is predicted to reach 14 million by the year 2050 (Mebane-Sims and Alzheimer's Association, 2009). Nowadays, there is not a definitive cure for this disease. Treatment and daily care of AD patients are considered costly in emotional and economical aspects. Available drugs used to treat AD are expensive, and they focus only to alleviate symptoms that are invariably fatal. The etiology of sporadic AD—more than 95% of cases—is not completely understood. The lack of knowledge about sporadic AD etiology makes it very difficult to prevent its onset and detect risk factors. Although the avoidance or prevention of modifiable risk factors may not have full impact in the future development of the disease, a recent study determined that good lifestyle habits and management of comorbidities may lead to a lower risk of dementia (Baumgart et al., 2015).

Therefore, identifying potential risk factors may facilitate a reduction in the burden of people affected by AD. In this review article, we will discuss proposed modifiable risk factors for AD, focusing on their effect on protein aggregation and deposition, and whether their prevention and control may have a direct impact in the potential to develop this dementia.

COMORBIDITIES

Vascular Diseases

The cerebrovascular network and the neurovascular control mechanisms have a pivotal role in maintaining the activity and integrity of the brain by assuring constant blood flow (Iadecola, 2004). In this process, the neurovascular unit—a specialized entity of neurons, astrocytes and vascular endothelial cells—has a crucial function. Alterations in this vascular system contribute to a reduction in global cerebral perfusion leading to brain dysfunction and cognitive impairment (Iadecola, 2013), thereby introducing the concept of the vascular hypothesis of AD. In this hypothesis, vascular pathologies promote the neuropathologic hallmarks of AD (de la Torre, 2018). Indeed, vascular risk factors are critically involved in the progression of dementia leading the conversion from mild cognitive impairment (MCI) to AD (Luchsinger et al., 2005; Li et al., 2011). Less than 10% of demented individuals develop only vascular dementia (Brenowitz et al., 2017). There is a growing body of evidence that supports the idea of vascular factors as contributors of the pathological mechanisms of AD. Epidemiologically, different risk factors for vascular diseases have been shown as significant risk factors for AD (Panpalli Ates et al., 2016). It has been suggested that the link between cerebrovascular disease (CVD) and AD is even much more important than the influence of aging (Love and Miners, 2016). Some of these common risk factors shared between CVD and AD are hypertension, diabetes, atrial fibrillation, atherosclerosis, hypercholesterolemia, and apolipoprotein E (ApoE) genotype (Vijayan and Reddy, 2016).

A history of prehypertension and hypertension in midlife or late in life increases the risk of developing dementia and enhances the neuropathology of AD (Dickstein et al., 2010; Gottesman et al., 2017a). The Honolulu-Asia study revealed that hypertensive patients showed an abundance of amyloid plaques and NFTs in the brain and atrophied hippocampus (Launer et al., 2000). Furthermore, high blood pressure promotes atherosclerosis in cerebral arteries, blocking the cerebral blood supply (Ninomiya et al., 2011), leading to lacunar or cortical infarcts, and, ultimately, cognitive impairment (Dickstein et al., 2010). Angiotensin-converting enzyme (ACE), that regulates blood pressure, is able to degrade A β (Hemming and Selkoe, 2005) and the use of anti-hypertensive medications, such as ACE inhibitors, to reduce the risk to develop AD may in fact lead to an opposite effect than desired. However, ACE inhibitors have been proven to not increase amyloid burden *in vivo* (Hemming et al., 2007). In humans, ACE inhibitors do not have a beneficial effect in cognitive impairment either (Peters et al., 2008), but other antihypertensive treatments may still be helpful to reduce

the risk of AD. Hence, hypertension could be established as one of the strongest risk factors for AD. On the other hand, it has been proposed that hypertension could be induced by the action of A β before dementia onset—being responsible for high blood pressure and cerebrovascular impairment (Petrovitch et al., 2000). Therefore, hypertension could be just a result of A β accumulation rather than a risk or a combination of both.

Hypertension is the main risk factor for stroke, a phenomenon that deprives the supply of blood flow to the brain. In fact, the severity of stroke is higher in diabetic patients, which increases the rate of death (Air and Kissela, 2007). Clinical history of stroke is associated with a prevalence of dementia, denoted as post-stroke dementia (Pendlebury and Rothwell, 2009), doubling the risk of developing AD in the elderly (Sun et al., 2006). Among single or multiple stroke patients, post-stroke dementia is a common outcome. Mechanistically, there are several processes that potentially link AD and stroke. It has been proposed that stroke could promote A β production, hamper A β clearance, and/or aggravate synaptic and neuronal loss already triggered by A β and tau pathology (Sun et al., 2008; Garcia-Alloza et al., 2011; Hongpaisan et al., 2011).

Heart disease (atrial fibrillation, arrhythmias, or cardiac arrest) causes a reduction in cerebral perfusion, leading to nerve cell damage (Kwok et al., 2011), brain dysfunction, and cognitive decline (Alosco et al., 2013). Atrial fibrillation is known as another risk factor for stroke, increasing the prevalence of AD and dementia (Ott et al., 1997; Kilander et al., 1998). The association between heart failure and cognitive impairment is supported by the induction of brain hypoxia and neuronal loss after a hypoperfusion event (Muqtadar et al., 2012). In addition, an elevation in A β 42 serum levels has been reported following a cardiac arrest episode, which would also contribute to AD neuropathology (Zetterberg et al., 2011). Overall, cardiovascular diseases seem to induce a lack of perfusion/oxygenation in the brain, leading to cognitive impairment and dementia mediated by an increase in A β levels due to different mechanisms. Although already existing A β aggregates can also induce cerebral perfusion impairment, a history of hypertension, stroke or heart disease can be considered a risk factor to develop AD.

The increased risk of developing AD dementia is also associated with atherosclerosis, a common vessel disorder in the elderly. AD patients show atherosclerosis in the circle of Willis (cerebral arterial circle at the base of the brain) much more severe and more frequently than healthy age-matched controls (Roher et al., 2003), and hypertension can have a role in promoting this intracranial atherosclerosis. This intracranial atherosclerosis reduces the brain blood perfusion and is linked to an increase in neuritic plaque burden and higher Braak stage in AD patients (Beach et al., 2007). Cholesterol has been consistently associated to AD. High levels of cholesterol have been linked to increased A β levels and greater cognitive impairment and progression in AD. Cholesterol seems to impair A β degradation and promote its production (Barbero-Camps et al., 2018). In fact, the use of statins, a cholesterol-lowering medication, such as simvastatin, has shown to lower the risk of AD diagnosis particularly in women (Zissimopoulos et al., 2017)

even in ApoE homozygotes (Geifman et al., 2017) and levels of phospho-tau in the cerebrospinal fluid (CSF; Li G. et al., 2017). The proposed mechanism is the direct interaction of statins and A β protofibrils (Shakour et al., 2019), inhibition of apoptosis (Hu et al., 2018). Therefore, hypercholesterolemia has been suggested to be a high-risk factor for AD and cholesterol-lowering medication should be considered as a preventive therapy for dementia.

Cerebral amyloid angiopathy (CAA) is a condition where A β deposits accumulate within the walls of the meningeal and intracerebral arteries, arterioles, and very rarely, veins and capillaries. This engenders a thickening of vessels walls and constriction of vascular lumen thereby promoting potential micro-aneurysms. This pathology increases the risk to develop hemorrhages, ischemic lesions, and encephalopathies, resulting in profound cerebral damage that contributes to neurodegeneration and cognitive dysfunction (Ellis et al., 1996; Haglund et al., 2006). CAA is associated to a more rapid cognitive decline in both demented and non-demented persons (Pfeifer et al., 2002). Certainly, CAA has a close association with AD and additive effects on the risk of developing dementia through AD pathology. The diagnosis of probable AD is related to the presence of CAA. In fact, CAA is highly prevalent in AD patients, being present in about 80%–90% of AD patients (Arvanitakis et al., 2011). Moreover, the role of hypertension has a significant additional causal factor that contributes to the progression of CAA-related vasculopathies.

Other CVDs have been described in the aging and AD brain supporting that cerebrovascular dysfunction contributes to neurodegeneration, cognitive dysfunction, and lowers the threshold for developing AD dementia. These cerebrovascular pathologies are cortical infarcts, lacunes, hemorrhages, microbleeds, intracranial small vessel atherosclerosis-arteriosclerosis, and blood brain barrier (BBB) dysfunction (Toledo et al., 2013). Generally, a higher number and the extent of cortical infarcts is directly associated with a higher risk of dementia. Extensive CAA and cerebral small vessel disease have also been proposed to contribute to neurodegeneration in AD (Toledo et al., 2013). Likewise, numerous microbleeds contribute to cognitive function decline and severe white matter lesions that lead to a 4-fold increased risk of developing MCI (Benedictus et al., 2015) that can eventually lead to AD development.

Regarding the effect of CVD on protein misfolding and deposition, there is a greater tendency of amyloid accumulation in patients with vascular risk factors (Langbaum et al., 2012; Gottesman et al., 2017b). Vascular insufficiency results in hypoperfusion and hypoxia that activate the amyloid precursor protein (APP) cleavage enzyme β -secretase (Xu et al., 2007) and facilitates a robust deposition of fibrillar amyloid. Therefore, A β not only promotes cerebrovascular dysregulation increasing the brain susceptibility to ischemia but also ischemia upregulates A β cleavage and its accumulation. On the other hand, the main A β clearance mechanisms are altered and damaged under the presence of vascular dysfunction contributing to parenchymal and vascular accumulation of A β (Garcia-Alloza et al., 2011). Tau hyperphosphorylation and NFTs are also associated with vascular risk and the synergistic effect of elevated A β burden

(Vemuri et al., 2017; Rabin et al., 2019). It has been also described that increased plasma levels of A β are linked to vascular disease both in the brain (white matter lesions and microbleeds) and in the periphery (hypertension, diabetes and ischemic heart disease; Janelidze et al., 2016). It should be noted that the contributions of vascular dysfunction occur at the early stages of AD pathophysiology and may represent a casual pathway towards dementia, facilitating an earlier diagnosis of AD. Furthermore, the vascular component is a promising target to decrease the risk of dementia and the neuropathological progression of AD. Nonetheless, further studies are required to elucidate the mechanisms underlying vascular pathologies as they relate to AD and dementia. This, along with the development of precise vascular biomarkers will be fundamental to discover new ways to prevent and treat AD and related dementias. Therefore, the improvement in the vascular health and the control of vascular risk factors may reduce the risk of developing vascular pathologies that trigger AD neuropathology.

Type 2 Diabetes

Diabetes is estimated to affect over 30.3 million people with over 7.2 million undiagnosed, and 90%–95% of these cases are delineated as type 2 diabetes (T2D; Centers for Disease Control and Prevention, 2017). T2D is a complex metabolic disorder that is characterized prominently by hyperinsulinemia, insulin resistance, glucose metabolism impairments, and, ultimately, pancreatic β -cell destruction. In T2D, pancreatic β -cells secrete excessive insulin in response to insulin resistance causing hyperinsulinemia, while allowing blood glucose levels (BGLs) to be maintained. As this continues over time, it begins to burden the β -cells, leading to insulin insufficiency and finally causing T2D. T2D and AD have a strong epidemiological link—so substantial that some researchers define AD as type 3 diabetes. T2D is proposed to increase the risk of AD and dementia from 1.3 up to 5.5 times and the Rotterdam study in the 1990s described T2D having double the risk for AD and dementia (Ott et al., 1999; Li et al., 2015). T2D patients are at ~60% greater risk for the development of dementia compared with individuals without diabetes (Chatterjee et al., 2016). Additional evidence of a systematic analysis concluded that T2D is convincingly a major risk factor for AD and vascular dementia (Bellou et al., 2017). There are simultaneous influences within each of these diseases that also adjoin T2D and AD, such as progressing age, diet, body mass index (BMI) and obesity, and sedentary lifestyle. In fact, adiposity, being overweight, or obese is a chief cause for insulin resistance (Luchsinger and Gustafson, 2009). There is a strong epidemiological link for T2D and AD and this may be due to their shared pathological mechanisms (Baglietto-Vargas et al., 2016).

Hyperinsulinemia has been associated with AD risk as indicated by such studies as the Honolulu-Asia Aging study (Luchsinger and Gustafson, 2009). Other than regulating the peripheral metabolism, insulin has insulin receptors expressed throughout the central nervous system (CNS). The function of brain insulin receptors is not clearly understood. It is known to regulate circuit function and plasticity by controlling synapse density and plays a role in the cholinergic system. Impairments

in insulin receptors and hyperinsulinemia have been associated with aging and AD. A decreased level in insulin receptors and their sensitivity in AD patients compared to middle-aged controls and expression and metabolism of A β and tau are also affected (Frölich et al., 1998; Sims-Robinson et al., 2010). Moreover, irregular insulin levels can disrupt the cholinergic system, which is also compromised in AD, as insulin aids in stimulating choline acetyltransferase (ChAT; Rivera et al., 2005). Insulin degrading enzyme (IDE) is vital for the degradation of insulin and A β . Thus, hyperinsulinemia can lead to a competition of insulin and A β for IDE, thereby increasing amyloid levels in the brain. Loss-of-function mutations of IDE in rodents exhibit glucose intolerance and accrual of A β aggregates, whereas, IDE action revealed opposite results (Shen et al., 2006). Downstream insulin signaling pathways are also affected. Pathways that are known to be involved in AD pathogenesis such as mitogen-activated protein kinase (MAPK), protein kinase B (Akt), and glycogen synthase kinase-3 β (GSK-3 β) are altered due to insulin dysregulation. MAPK expression is correlated with A β production and NFTs and is increased in AD patients. Under insulin resistance, Akt signaling can inhibit GSK-3 β , which dephosphorylates and activates glycogen synthase in glycogenesis and ultimately resulting in the hyperphosphorylation of tau. Accordingly, the cognitive impairment that is noted in both T2D and AD could be intervened by insulin administration. Tied to insulin issues is the dysfunction of glucose metabolism. The brain is estimated to consume 20% of energy stored in the body, and neurons depend on a steady peripheral transport of glucose through the BBB facilitated by glucose transporters (GLUTs), especially GLUT-1 and -3. Deficiency in GLUT-1 and -3 is reported in AD brains, and this decrease correlated to the decrease in O-GlcNAcylation, hyperphosphorylation of tau, and to the density of NFTs (Liu et al., 2008, 2009). Indeed, imaging techniques such as Fluorodeoxyglucose (FDG)-PET imaging are able to detect glucose metabolism alterations in AD related to anatomical areas associated with pathology and preceding cognitive impairments (Ballard et al., 2011; Nordberg, 2015).

Both AD and T2D are diseases related to protein misfolding and aggregation (Soto, 2003; Moreno-Gonzalez and Soto, 2011; Morales et al., 2013). In T2D, the aggregation of an amyloidogenic protein called islet amyloid polypeptide (IAPP) or amylin is seen in up to 96% of T2D patients in pancreatic β -cells (Clark et al., 1995; Westermark, 2011). IAPP is a hydrophobic hormone co-secreted with insulin into blood circulation at 1:100 ratio. It contributes to glycemic control by slowing down gastric emptying and inhibiting digestive secretion and other pancreatic hormones. Although it is not clear that IAPP is a cause or an effect of T2D, amyloidogenic IAPP aggregates are toxic and have been proposed to destroy β -cells and facilitate the progression of the disease (Westermark, 2011; Abedini et al., 2015). In fact, genetically modified rodent models expressing human IAPP demonstrate aggressive diabetic-like phenotype, such as insulin impairments and hyperglycemia, with IAPP deposits and β -cell loss (Clark et al., 1995; Janson et al., 1996). Interestingly, IAPP has been discovered in AD brains, whereas A β and tau have been found in T2D pancreas; in

addition, these proteins were seen to co-localize in brain and pancreas (Miklossy et al., 2010; Valente et al., 2010; Moreno-Gonzalez et al., 2017). Moreover, T2D patients display increased amounts of NFTs and A β in the hippocampus (Miklossy et al., 2010). In AD patients, there is an extensive prevalence of IAPP compared to non-AD (Janson et al., 2004). Brain of T2D/AD patients show an augmented number of cortical A β plaques and tau-positive cells compared to affected AD brains suggesting that T2D/AD patients have a more severe pathology with much more rapid progression (Bretherton-Watt and Bloom, 1991). Therefore, these amyloidogenic proteins may interact directly. IAPP [8–18] and IAPP [22–28] sequences were noted hot regions for IAPP and A β 40 interaction (Kapurniotu et al., 2010). One proposed mechanism is the cross-seeding of A β and IAPP when oligomers composed by one protein seed the aggregation of a different protein by a seeding-nucleation process (Morales et al., 2013; Jucker and Walker, 2015; Moreno-Gonzalez et al., 2017). Many studies reveal a successful heterologous seeding aggregation when both proteins are present *in vitro* (Berhanu et al., 2013; Yan et al., 2014; Moreno-Gonzalez et al., 2017). Double transgenic mice overexpressing both A β in brain and IAPP in pancreas show increased A β burden compared to controls (Moreno-Gonzalez et al., 2017). IAPP pancreatic homogenate injected into an AD mouse model provided a potent seeding effect by accelerating AD pathology and impairing memory (Moreno-Gonzalez et al., 2017). Independently of the mechanism of action, T2D can be considered one of the main risk factors for AD.

Traumatic Brain Injury

Recent research has posited that traumatic brain injury (TBI) is a robust factor that leads to the advancement of AD or dementia. The severity of TBI is quantified by the Glasgow Coma Scale (GCS). Severe TBI (sTBI) represents head injuries that result in permanent or an extended period of unconsciousness, amnesia, or death following a head injury with a GCS of 3–8. Moderate TBI involves a period of unconsciousness or amnesia from 30 min \geq 24 h with a GCS of 9–12. Mild TBI (mTBI) is recognized as head injuries that cause a brief state of altered consciousness resulting in \leq 30 min of unconsciousness, though most mTBIs do not result in a loss of consciousness. mTBI represents a majority of reported cases and has been linked to AD pathology (Edwards et al., 2017). The harsher the TBI the greater risk of developing AD (Graves et al., 1990; Guo et al., 2007). World War II veterans that had a TBI event had an increased risk of developing AD (Plassman et al., 2000). After a TBI event, dementia diagnosis was found to be strongest within the first year (4–6 times) but maintained significance up to 30 years (Nordström and Nordström, 2018). In a large cohort study, the overall risk of dementia in individuals with a history of TBI was 24% higher than those without a history of TBI. A sTBI increased AD risk by 35% and a single mTBI or concussion increased the risk by 17%. The risk of dementia was increased with the number of TBI events—33% higher for two or three TBIs, 61% higher for four TBIs, and 183% higher for five or more TBIs (Fann et al., 2018), demonstrating the link between TBI severity

and the number of events and dementia. TBI begins with an instant, irreversible initial blow or impact causing direct damage to the surrounding neuronal and astroglial cells and vasculature. Primary insult can either be a focal injury or diffuse axonal injury (DAI). The impact can trigger a rapid necrosis due to the mechanical damage, edema, increased intracranial pressure, and ischemia. This will secondarily lead to neuronal excitotoxicity, mitochondrial dysfunction, oxidative stress, inflammation, synaptic dysfunction, axonal degeneration, neuronal death, and, ultimately, instigating cognitive and behavioral impairments (Gentleman et al., 2004; Breunig et al., 2013). Therefore, TBI shares many of the molecular mechanisms observed in AD. Following TBI, multiple cell death pathways get activated leading to synapsis reduction and finally neuronal loss as loss of total brain volume in the hippocampus, cortex and other medial temporal lobe structures, and elevation in ventricular volume has been described (Blennow et al., 2016). This neurodegenerative process initiated by TBI may trigger the development of memory problems that may then convert into AD.

Numerous *in vivo* studies demonstrate A β and tau pathophysiology along with other pathological consequences alike to AD following TBI. A β plaques are reported in up to 30% of post-mortem TBI patients. A β can accumulate rapidly following TBI, reported as early as 2–4 h (Graham et al., 1996). Plaque formation is described as diffuse plaques seen in early-stage AD and seen in all ages, even children, but determined to be more robust in elderly affected individuals (Johnson et al., 2012). Post-mortem TBI brains show greater A β density compared to age-matched controls years following injury (Johnson et al., 2012). Notably, A β 42 is seen to be the major type following a TBI event in brain and CSF (Breunig et al., 2013). Interestingly, A β can accumulate in the white matter following TBI, unlike AD where it is more prominent in gray matter. It is described that the key constituents that generate A β (APP, β -secretase, and γ -secretase) anomalously colocalize at swollen and disconnected axonal bulb sites, producing and releasing A β into the brain parenchyma (Chen et al., 2009). Repetitive mTBI is associated to other tauopathies, especially to chronic traumatic encephalopathy (CTE). NFT pathology was found in 8 out of 27 post-mortem TBI brains (Smith et al., 2003). In fact, widespread NFTs are present in up to a third of patients following survival of a year or more from a single TBI (Johnson et al., 2012). Tau levels in CSF from TBI patients expressed over a 1,000-fold increase compared to various neurological-diseased and non-diseased individuals (Zemlan et al., 1999). Alterations of multiple protein kinases and phosphatases, neurofilament proteins, APP, BACE1, and even aggregated α -synuclein have been also found after TBI (Uryu et al., 2007). Therefore, TBI induces disease processes that may accelerate the formation and aggregation of misfolded proteins, possibly through axonal damage, and perhaps building upon the pathogenesis of AD.

Epilepsy

Epilepsy can be defined as a neurological disorder where there is a continual and spontaneous propensity to have seizure activity as convulsions or non-convulsions due to abnormal

neural firing and networks. Genes, developmental mechanisms, injury insult, and neuronal plasticity are thought to play chief roles in epilepsy (Scharfman, 2007). The convoluted functional neuronal network imbalances in epilepsy can ultimately result in neuropathological changes, brain atrophy, and cognitive decline (Friedman et al., 2012). It is not known if epileptic seizures are a cause or an effect of AD, but certainly, they both share mutual molecular and cellular mechanisms (Bazil, 2003). MCI and early-stage AD patients with epileptic activity show earlier onset of AD and accelerated rate of cognitive decline (Vossel et al., 2013, 2016; Cretin et al., 2016). On the other hand, multiple studies indicate that AD patients have an elevated risk of developing seizures or epilepsy (Vossel et al., 2016). Indeed, the pervasiveness of seizures is about 7–8 fold higher in individuals with AD than individuals without dementia (Amatniek et al., 2006). Additional studies posit that the younger the age of dementia onset is correlated to increased seizure risk, as well as the severity or stage of AD, has a parallel relationship with seizure (Horvath et al., 2016). Seizures are commonly described in cases of familial AD and strongly related to Down syndrome cases. Thus, epileptic seizures could be an early event in AD progression or an integral part of AD severity. However, more studies are needed as a systemic database meta-analysis between dementia and epilepsy concluded significant gaps of knowledge in epidemiology between the two disorders with insufficient data to pool an overall incidence rate.

Central neural circuits maintain a mean firing rate related to constant, spontaneous neuronal activity, which is dependent on intrinsic circuit excitability, and their synaptic properties and functional connectome. Firing instability and limited synapse flexibility at early AD stages trigger a vicious cycle and dysregulation of an integrated homeostatic network (Frere and Slutsky, 2018). Firing rates also can be dependent on the balance of excitation and inhibition ratio, and its imbalance could play a role in AD and epilepsy. Hyperexcitability can be triggered by the mismanagement of glutamate levels and Ca²⁺ homeostasis in the brain. Glial cells could also play a role in hyperexcitability and seizures as induced seizures are shown to excite astrocytes directly by stimulating the release of glial glutamate (Ding et al., 2007). Phase-coupling of oscillations in the brain is central for normal brain function. Gamma oscillations (30–150 Hz) are known to increase locally for sensory processing and memory encoding, while other oscillations would be reduced accordingly, such as alpha, beta, and theta. AD patients exhibit reductions in gamma power oscillations. Pharmacological inhibition of gamma oscillations leads to augmented epileptic activity in experimental animals (Maheshwari et al., 2016). Gamma oscillations can be increased by social interactions and mental stimulation; therefore, these activities have been suggested as a preventative measure in AD development. Antiepileptic treatments, such as levetiracetam, reverse neural network impairments and behavior (Sanchez et al., 2012), decrease brain dysrhythmia (Das et al., 2018), and improves cognition in animal models and MCI patients (Bakker et al., 2012).

A plethora of AD transgenic animal models reveals stochastic epileptiform. In general, A β is thought to induce neuronal hyperexcitability by differentially attacking excitatory and

inhibitory neurons. A β can affect nACh, N-Methyl-D-aspartate (NMDA), and AMPA receptors, and calbindin pathways (Corbett et al., 2017). In APP23xPS45 mice, neuronal hyperexcitability occurs before any A β plaque deposition. Inhibition of oligomeric A β restores neural activity while inoculation of oligomeric A β in wild-type mice induces hyperexcitability (Busche et al., 2008). AD Tg mice also reveal cortical hyperactivity near amyloid plaques due to decreased GABAergic inhibition. APP/PS1 mice have early-impaired GABAergic interneurons in the hippocampus and entorhinal cortex (Ramos et al., 2006; Moreno-Gonzalez et al., 2009; Baglietto-Vargas et al., 2010). Administration of A β suppresses gamma oscillations *in vivo* and *in vitro* (Mucke and Selkoe, 2012). The chronic presence of A β and hyperexcitability effect could have an indirect effect by exhausting inhibitory neurons resulting in their deterioration. On the contrary, vulnerable neural networks produced by epileptogenic episodes could aid in the triggering of A β plaques. Chronic neural stimulation promotes amyloid deposition and elicits epileptic activity in an AD mouse model (Yamamoto et al., 2015), as well as increasing firing rate has been noted to surge A β production (Kamenetz et al., 2003). Tau protein could play a much larger role in neuronal activity and, therefore, epileptiform activity than previously thought. Epileptic patients present elevated levels of total tau in CSF (Monti et al., 2015). In fact, pharmacologically induced epilepsy in 3xTg-AD mice leads to elevated hyperphosphorylated tau levels in the dentate granule cells and mossy fibers (Yan et al., 2012), indicating the effect of epileptic activity in tau misfolding and aggregation. Moreover, synaptic activity can stimulate the release of tau and spreading of tau pathology, induce tau phosphorylation, and relocate tau to the dendritic spines (Khan et al., 2014; Frandemiche et al., 2014; Wu et al., 2016). On the other hand, reduction of tau protein levels prevents cognitive decline, synaptic impairment, and spontaneous epileptiform activity in several APP mouse models (Roberson et al., 2011; de Calignon et al., 2012). A152T tau transgenic mice present abnormal brain oscillations (Das et al., 2018), suggesting a mutual effect of epileptic activity and tau aggregation. Nevertheless, future studies are needed to elucidate epileptiform activity in the etiology and progression of AD; however, current research dictates a strong relationship between epilepsy and AD.

Depression

Depression, also termed major depressive disorder, is a serious medical illness with a wide range of mental health issues that affects about 300 million people worldwide (World Health Organization, 2017). This disease is characterized by feelings of sadness and loss of interest in ordinary things. A common triad of symptoms seen include anhedonia, low energy or fatigue, and a low or depressed mood. Depression is a common symptom seen in people suffering from AD (Drevets and Rubin, 1989; Lyketsos et al., 1996). There is a debate whether depression is a risk factor for developing AD, rather than just a symptom. Recently, several clinical studies bolstered the idea of depressive symptoms as a crucial risk factor for cognitive decline and AD. It has been shown that the age of onset for AD is expedited

in MCI patients with a history of depression (de Oliveira et al., 2015). In fact, there is a strong association between depression and AD onset (Barnes et al., 2012; Steenland et al., 2012). In addition, a less studied area between depression and AD is whether the age of onset of depression could lead to a different pathology of AD. Early-life depression (ELD) is characterized as onset before the age of 60 as opposite to late-life depression (LLD), so there is interest to determine how the age of onset of depression would influence the progression of AD. It remains to be elucidated if depression onset, whether ELD or LLD, could influence the progression of AD or even engender disparate pathology in AD. Large-scale prospective studies proposed that LLD, but not early or mid-life, increases the risk of AD (Barnes et al., 2012). These findings were confirmed by a recent meta-analysis study suggesting LLD increases the risk of AD incidence by 1.65-folds (Diniz et al., 2013). Moreover, a recent study reported elevated A β deposition in patients with a lifetime history of major depression (Li P. et al., 2017). Additionally, individuals with MCI plus coexistent depressive symptoms have an elevated A β load and a higher risk of faster conversion to AD compared to non-depressed MCI patients (Hebert et al., 2013).

Neurotransmitters like dopamine and serotonin play a crucial role in both the development of depression and in AD pathology (Chen et al., 1996; Jacobsen et al., 2012). Serotonin helps regulate mood, social behavior, and memory, whereas, dopamine, functions in motor control and reward-motivated behavior. Therefore, these two neurotransmitters could be key in the conversion of depression into AD. In AD mice, dopaminergic neuronal loss in the midbrain leads to memory impairment (Nobili et al., 2017), whereas restoration of dopamine release improves cognitive dysfunction (Guzman-Ramos et al., 2012). In depression, there is a decrease in dopamine production leading to a loss of reward-motivated and low levels of serotonin have been associated with depressive behavior since serotonin regulates mood and social behavior. Additionally, selective serotonin reuptake inhibitors or SSRIs reduce brain A β levels by increasing serotonin levels in the brain (Nelson et al., 2007).

Many factors can lead to the onset of depression, but the most studied cause is stress (Monroe et al., 2007; Ross et al., 2018). Stress works by activating the hypothalamus-pituitary-adrenal (HPA) axis leading to the release of glucocorticoid hormones from the adrenal cortex—cortisol in humans and corticosterone in rodents (Caruso et al., 2018). Rising levels of cortisol can negatively affect the HPA axis and refrain it from maintaining its sensitivity and regulating the stress response. Increased cortisol levels have been seen in biological fluids of patients affected by AD (Hatzinger et al., 1995; Rasmuson et al., 2001; Curto et al., 2017). Stress increases the production of A β and enhances the formation of amyloid plaques by increasing corticotropin-releasing factor release, which leads to an increase in neuronal activity, stimulating the production of A β , and demonstrating a link between depression and AD development (Dong and Csernansky, 2009). In addition, stress induces neuronal loss in the hippocampus, an area known to be one of the earliest regions affected by AD neuropathology, by increasing glucocorticoid release and

decreasing neurotrophic factors (Kumamaru et al., 2008). Oral administration of corticosterone leads to morphological changes in the hippocampal region of rats, adding to the idea that stress triggers directed neurodegeneration (Magariños et al., 1998). Recently, patients suffering from LLD presented a faster hippocampal atrophy rate than those with ELD, eluding that LLD, and not ELD, leads to a higher risk of developing AD. Therefore, there may be a different progression of the disease depending on the age of depression onset (Taylor et al., 2014), and LLD could be considered a risk factor for AD development. The effect of taking antidepressants on AD pathology and development before the onset of the disease as a preventive therapy in LLD population remains to be determined.

LIFESTYLE

Physical Activity

Under normal circumstances, an elderly individual without dementia diagnosis will exhibit hippocampal volume shrinkage of 1%–2% each year (Erickson et al., 2011). Hippocampal shrinkage may be reversed by a moderate-intensity exercise training. A 1-year aerobic exercise intervention was effective at increasing hippocampal volume by 2% and offsetting normal decline associated with aging (Erickson et al., 2011) and individuals with life-long exercise routine reveal larger brain volume and improved executive function than inactive older adults (Tseng et al., 2013). However, the increase in volume was selective since it only influenced the anterior hippocampus including the dentate gyrus, in which cell proliferation occurs. Clinical studies indicate that physical activity may be neuroprotective by preserving cognition and maintaining the brain neuroplasticity (Kramer et al., 1999; Winter et al., 2007). In addition to prevention, exercise has shown to have a favorable outcome on improving cognitive symptoms. AD patients performing a moderate exercise program for a year exhibited a slower decline in the capability to achieve activities of daily living and amelioration on the physical impairment (Rolland et al., 2007; Pitkälä et al., 2013). Some other studies have also found that aerobic exercise is able to improve memory performance and cognitive function in aging, MCI, and AD patients (Baker et al., 2010; Vidoni et al., 2012; Morris et al., 2017). Although all these studies indicate that exercise may be effective in reducing the clinical symptoms observed in AD patients, there are no studies reporting its effect on amyloid deposition and how physical activity may prevent from developing AD in at risk population. In this direction, several studies have intended to investigate the beneficial effects of exercise on cognitive function and amyloid deposition in AD models. Streptozotocin-induced mice where placed on treadmill exercise daily for 30 min for a month. Afterwards, rats showed a decline in amyloidogenesis and tauopathy as well as a suppression of neuroinflammation and oxidative stress leading to selective anti-inflammatory microglia activation and pro-inflammatory microglia inhibition, hippocampal neuroprotection, and overall cognitive preservation (Lu et al., 2017). In transgenic animal models of AD, exercise leads to amelioration of behavior

impairment, reduction of A β deposition, larger hippocampal volume and decreased apoptosis (Adlard et al., 2005; Nichol et al., 2007; Um et al., 2008; Liu et al., 2013), especially in animals under a voluntary exercise routine (Yuede et al., 2009). Enhanced cognitive function was also observed in ApoE ϵ 4 mouse models (Nichol et al., 2009). Likewise, Tau transgenic animals subjected to forced or voluntary treadmill exercise for several months show reduced levels of total tau, ptau and insoluble tau, although it had no neuroprotective effects (Leem et al., 2009; Belarbi et al., 2011; Ohia-Nwoko et al., 2014). Likewise, exercise decreases BACE (secretase beta-site APP cleaving enzyme-1) activity and APP levels compared to sedentary rats (Alkadhi and Dao, 2018). Regarding neuroprotection, both treadmill and swimming exercise are able to decrease caspase-3 expression and reverses the Bax to Bcl-2 ratio observed in AD (Jin et al., 2014; Baek and Kim, 2016). Treadmill exercise also increases sirtuin-1 (SIRT-1), a modulator of neuronal survival, in a transgenic AD mouse (Koo et al., 2017) and enhances spatial memory in AD mice through upregulation of c-Fos, an indicator of neuronal activity expressed after depolarization (Jee et al., 2008).

Brain-derived neurotrophic factor (BDNF) serves as a mediator in neurogenesis as well as dendritic expansion, playing a vital role in memory formation. Acute exercise increases BDNF production in the brain (Neeper et al., 1995; Ferris et al., 2007). Modifications in BDNF serum correlate with changes in the hippocampal volume in MCI and Borba et al. (2016). AD models exposed to treadmill exercise show promotion of cell proliferation and amelioration of memory impairment observed by an increase in BDNF and TrkB levels (Liu et al., 2011; Kim et al., 2014; Sim, 2014). BDNF also enhances non-amyloidogenic APP processing by activating α -secretase and, therefore, reducing the amount of toxic A β peptides after voluntary exercise (Nigam et al., 2017). A recent report suggests that additional stimulation of adult hippocampal neurogenesis and increase in BDNF levels is necessary to induce the cognitive beneficial effect of exercise (Choi et al., 2018). Irisin is a myokine that is also released by physical exercise (Wrann et al., 2013). FNDC5/irisin prevents the binding of A β oligomers to neurons reducing its toxicity *in vitro* whereas irisin knockout mice present a deterioration in long-term potentiation and memory. In AD brains, irisin levels are reduced positing this myokine as a mediator of the beneficial effects of exercise in preventing or reducing the deleterious effects of AD pathology (Lourenco et al., 2019). Therefore, recent reports suggest that physical activity has a positive effect on synaptic plasticity, hippocampal shrinkage, and memory formation in animal models and, moreover, it can decrease the load of amyloid aggregates. Studies performed in AD patients indicate that exercise ameliorate some of the AD-related clinical symptoms and helps to decrease the progression of the disease. It still remains unknown whether exercise could diminish the risk to develop AD although studies performed in MCI patients may shed light to its potential benefits for prevention.

Sleep Disturbance

The sleep-wake cycle refers to a 24-h daily sleep pattern, typically consisting of 16 h of being awake and 8 h of sleep. This

cycle, controlled by the body's circadian rhythm and sleep homeostasis, is important to many brain functions and plays a role in removing toxins from the brain that have accumulated throughout the day. A sleep cycle consists of stages N1, N2, and N3 non-rapid eye movement (NREM) sleep followed by REM sleep. During REM sleep, the brain is highly active as it is being rewired and is considered the most important part of the sleep-wake cycle. With aging, the sleep pattern is altered by a reduction in sleeping time and REM sleep. Sleep-wake cycle disturbances, including increased daytime sleep, reduced nocturnal sleep, and sleep fragmentation, are a common feature seen in AD patients (Bonanni et al., 2005; Moran et al., 2005). It is well established that in AD patients electroencephalograms are characteristic of increases in N1 and N2 NREM sleep and REM latency, and decreases in REM sleep, leading to an overall decrease in sleep duration (Loewenstein et al., 1982). Recent studies indicate that prolonged sleep duration could be indicative of at risk population (Westwood et al., 2017) and, in fact, NREM characteristics may provide evidence of an already deteriorated cognitive condition (Taillard et al., 2019). Due to the association between aging, cognition and sleep disorders, it has been proposed that sleep disturbances may lead to an increased risk for AD development (Roh et al., 2012). In fact, disorders in the sleep pattern have been related to an increased risk to develop cognitive deficiency, including MCI and dementia (Diem et al., 2016). On the other hand, deposition of A β seems to deteriorate sleep efficiency (time in bed spent asleep), especially during the preclinical stage (Ju et al., 2013).

An increase in the amount of light throughout the sleep-wake cycle leads to an increase in insoluble tau and memory impairment since continuous light input suppresses the production of the hormone melatonin that regulates the sleep-wake cycle (Di Meo et al., 2014). It has been shown that sleep increases the rate of A β clearance in the brain through the glymphatic system (Xie et al., 2013). In fact, the interstitial concentration of A β was higher in awake humans when compared to sleeping ones, indicating that wakefulness is associated with an increased production of A β (Bateman et al., 2006). The glymphatic system is able to clear waste products through convective bulk flow of interstitial fluid (ISF) that is facilitated by astrocytic aquaporin 4 (AQP4) water channels. Moreover, removal of these AQP4 channels led to reduced clearance of A β by 65%, suggesting the importance of these channels in removing unwanted waste from the brain (Iliff et al., 2012). During sleep, there is an increase in the interstitial space, which leads to an augmentation in the exchange between CSF and ISF, facilitating A β clearance. In fact, just one night of acute sleep deprivation increases the levels of A β in the brain, independently of ApoE genotype, indicating the direct effect of sleep in AD pathology (Shokri-Kojori et al., 2018). Additionally, sleep also led to a decrease in ISF tau levels, shown by ~90% increase during wakefulness and ~100% increase during sleep deprivation (Holth et al., 2019). Moreover, these results were also seen in the CSF of patients who were sleep deprived, leading to a 50% increase in CSF tau levels. Changes in sleep precede the onset of cognitive symptoms seen in AD

patients, and sleep-wake cycle disturbances are proposed as one of the earliest symptoms seen in AD. Thus, disruptions in the sleep-wake cycle could be considered a risk factor for AD and early management of sleep-wake cycle disturbances could prevent or slow the subsequent pathology and later onset of AD. Several strategies can be considered to modulate the effect of sleep disturbances in dementia risk, from sleep drugs to physical exercise (McCleery et al., 2016; Law et al., 2019). Orexin is a neuropeptide that regulates wakefulness and is implicated in various sleep disorders, such as narcolepsy and cataplexy. Treatment to effectively block orexin receptors mitigated brain ISF levels of A β that were elevated due to wakefulness or sleep deprivation in AD mice (Kang et al., 2009; Roh et al., 2015).

Diet

Compiling evidence suggests that a Mediterranean diet (MeDi) or Mediterranean-Dietary Approaches to Stop Hypertension diet (MIND) reduce the risk of developing MCI or AD (Morris et al., 2015). MeDi is highly popular on its preventive effects on AD (Scarmeas et al., 2007). A MeDi consists of a low intake of saturated fatty acids, such as meat and poultry; a low-to-moderate consumption of dairy products, such as cheese and yogurt; a moderate amount of alcohol, such as wine; and a high intake of vegetables, legumes, fruits, cereals, fish and unsaturated fatty acids. Studies performed in Spain, France, North America, and recently in Australia, demonstrated that the higher the adherence to a MeDi lowered the risk to contracting diseases associated as risk factors for AD (Tangney et al., 2011; Gardener et al., 2012) and protects against cognitive decline in elderly population, specifically episodic memory and global cognition (Trichopoulou et al., 2015; Valls-Pedret et al., 2015; Loughrey et al., 2017), indicating that MeDi may reduce Alzheimer's risk. A 3-year brain imaging study evaluated the effects of a low to a high adherence MeDi on AD biomarkers in 30–60-year-old cognitive normal participants. The study concluded that a higher MeDi adherence provided an average of 1.5–3.5 years of protection against AD as well as a lower adherence highlighted important AD biomarkers (Berti et al., 2018). MeDi has been shown to reduce oxidative stress by decreasing intracellular reactive oxidative species, apoptosis, and cells containing telomere shortening. Elderly patients adhering highly to MeDi demonstrated longer telomere length and high telomerase activity (Boccardi et al., 2013), and high intake of vegetables is also directly associated with longer telomere length (Gu et al., 2015). Several studies point out that the polyphenols found in the characteristic olive oil in the MeDi regimen are the main active components to prevent AD (Omar et al., 2018). Oleuropein aglycone, present in extra virgin olive oil, induces autophagy, decreases the amount of aggregated proteins, decreases inflammation, and improves cognitive function seen in AD (Grossi et al., 2013; Cordero et al., 2018). Hydroxytyrosol, another olive oil product, has antioxidant and anti-inflammatory properties. In APP/PS1 mice, hydroxytyrosol administration reduces mitochondrial oxidative stress, neuronal inflammation and apoptosis (Peng et al., 2016).

On the contrary, a high-fat diet (HFD) raises the risk of developing obesity, leading to increased chances to develop diabetes and, therefore, promoting the development of cognitive deficits, and perhaps AD. A HFD consists of a regimen where the majority of the calories ingested come from a fat source rather than carbohydrates or protein. AD transgenic mice fed using HFD for 4 months presented significant memory impairment compared with AD mice eating regular diet (Sah et al., 2017). There were no differences in the levels of A β or ptau suggesting that HFD induces cognitive impairments in an amyloid-independent pathway. In fact, HFD has shown to accelerate age-associated cognitive decline by decreasing BDNF levels, inducing oxidative stress, and generating a loss in synaptic plasticity (Thériault et al., 2016).

As already mentioned, insulin resistance, impaired glucose metabolism, and T2D are well known risk factors for AD. These conditions can be developed following a diet of high sugars, carbohydrates and glycemic loads. High-glycemic diet includes: high-sugar beverages and foods, white pasta and rice, French fries and baked potatoes, cereals with added sugar, and sundried fruit. A high-glycemic regimen correlates with an increment in A β accumulation before AD manifestation (Taylor et al., 2017). Consumption of fish oil and an omega-3 fatty acid-rich diet decreases plasma arachidonic acid/docosahexaenoic acid (AA/DHA) ratio levels. MCI and AD patients carrying ApoE ϵ 4 present increased AA/DHA ratio compared to carriers who did not present any cognitive deficiencies (Abdullah et al., 2017). DHA demonstrates a pleiotropic effect by balancing cell signal pathways, synaptic plasticity, and the enzymatic processing of A β (Davinelli et al., 2012). Fish oil/omega-3 fatty acid was correlated with a decline in AA/DHA levels and even in AD-ApoE ϵ 4 patients (Abdullah et al., 2017), indicating that omega-3 supplementation could be considered as an intervention against the risk of acquired AD, especially in ApoE ϵ 4 carriers. Whole food diet (WFD) consists of freeze-dried fish, fruits, and vegetables. AD mice fed with the WFD were highly impaired in spatial memory compared to controls and produced an elevated neuroinflammatory response (Parrott et al., 2015).

A large body of literature suggests that a balanced diet, full of fruits, vegetables, and lean meat and fish along with low sugar and high good fat content may be beneficial against cognitive impairment and, therefore, decrease the chances to develop AD. However, recent studies have found no significant association between dietary patterns, including MeDi, and risk for dementia (Haring et al., 2016; Akbaraly et al., 2019), indicating that adherence to healthy dietary patterns may not be enough to reduce the risk to develop age-related cognitive impairment and dementia.

Smoking

Worldwide, approximately 1 billion people use tobacco products in the form of cigarettes, and annually, there are at least 6 million global deaths caused by tobacco-smoking related diseases (World Health Organization, 2013). Today, smoking-related incidence has expanded from including CVD and stroke to now including neurocognitive abnormalities (Swan and Lessov-Schlaggar, 2007;

Durazzo et al., 2010). Smoking leads to cognitive impairment and decline shown by faster declines in verbal memory and slower visual search speeds (Richards et al., 2003). Additionally, cognitive decline in smokers is directly proportional to the number of packs they smoke per day (Kalmijn et al., 2002). Indeed, it is known that smoking has negative effects on cardiovascular diseases which, as mentioned, are risk factors of AD, stressing out the deleterious importance of smoking in promoting dementia.

Historically, smoking has been considered a preventative measure from developing AD as many have stated that nicotine improves short-term cognitive performances and inhibits amyloid formation (Brenner et al., 1993; Lee, 1994). Actually, nicotine has been proven to reduce APP secretion (Lahiri et al., 2002), inhibit A β aggregation (Dickerson and Janda, 2002), and reduce A β load in AD transgenic mice independently from inflammation (Nordberg et al., 2002; Hellström-Lindahl et al., 2004). However, more recent studies have questioned this evidence and indicate that smoking increases the chance to develop dementia and cognitive decline (Ott et al., 1998; Anstey et al., 2007; Reitz et al., 2007). Confirming this negative effect, nicotine exacerbates tau phosphorylation in experimental animals (Oddo et al., 2005). In addition, exposure to cigarette smoke exacerbates Alzheimer's-like pathology by increasing amyloid deposition, inducing tau hyperphosphorylation, and exacerbating the inflammatory response in a smoke-consumption concentration dependent manner (Moreno-Gonzalez et al., 2013). Still some studies indicate that when epidemiological data is adjusted for competing risk of death without dementia, smoking seems not to be associated with dementia development (Abner et al., 2018), and, surprisingly, ApoE ϵ 4 carrier smokers are at a lower risk of developing dementia than smokers without this allele (Reitz et al., 2007). The mechanism by which smoking may lead to an increased risk in AD development is uncertain, and further studies need to be conducted for potential mechanisms responsible for a possible increased risk of AD development.

Alcohol

Alcohol consumption is considered a major risk factor for many health problems. Heavy drinking is defined as: consuming more than four drinks a day (or 14 drinks a week) for males and consuming more than three drinks a day (or seven drinks a week) for females (Rehm, 2011). Knowing that alcohol negatively affects cognitive and motor functions, there is no surprise that heavy drinking has been associated with an increased risk of AD, whereas mild to moderate alcohol intake has been associated with a lower risk (Heymann et al., 2016). The extent to which alcohol affects AD pathology is still debated today as some believe that alcohol is protective of AD development (Luchsinger et al., 2004), while others believe the contrary (Piazza-Gardner et al., 2013), the latter being the strongest current of opinion. Heavy alcohol consumption leads to a decline in cognitive performance similar to that observed in AD (Weissenborn and Duka, 2003). Loss of cholinergic neurons observed in AD patients has also been reported in individuals exposed to ethanol consumption (Fernandez and Savage, 2017;

Vetreno and Crews, 2018) as well as hippocampal atrophy (Topiwala et al., 2017), linking heavy alcohol consumption with cognitive impairment that may eventually trigger AD development. In fact, a combination of both smoking and drinking can have a more impactful effect of AD incidence than just one of those habits (Zhou et al., 2014). Some recent reports indicate that alcohol use is not associated with prodromal AD or disease progression (Heffernan et al., 2016; Bos et al., 2017). In addition to the potential link to trigger dementia, alcohol abstinence after AD diagnosis seems to ameliorate the cognitive damage initially observed (Toda et al., 2013), suggesting the alcohol consumption can, not just increase the risk of AD, but also worsen the progression of the disease in heavy intake conditions (Heymann et al., 2016). A potential mechanism proposed for alcohol to induce AD is by decreasing glymphatic function (Lundgaard et al., 2018). The glymphatic system plays an important part in removing brain waste, including A β . Since alcohol decreases glymphatic function, heavy drinking could induce A β accumulation by reducing its clearance triggering the cognitive abnormalities that are seen in alcohol use and AD.

On the other hand, alcoholic beverages such as wine—particularly red—contain polyphenols including morin, quercetin, resveratrol, and tannins, that are able to inhibit amyloid aggregation and can have other beneficial effects including reduction of oxidative stress, inflammation, and balance of protein homeostasis (Dhouafla et al., 2018). In fact, moderate drinking (1–2 drinks/day) has been proposed to be protective against AD by reducing amyloid burden, decreasing mortality, and reducing the risk of dementia (Russo et al., 2003; Deng et al., 2006; Wang et al., 2006), being low doses of wine the most recommended to reduce the risk of dementia (Xu et al., 2017). In AD animal models, low doses of ethanol decrease A β -mediated synaptic toxicity by direct interaction with A β peptide (Muñoz et al., 2015). This may be an indication that the amount (drinks/day), length of consumption, period of consumption (early or late life), and type of alcoholic beverages (fermented or distilled drinks) should be taken into consideration to determine the effect of alcohol consumption to protect or induce AD dementia.

CONCLUDING REMARKS

Despite over a century since discovering AD, there is no cure that can halt, slow down, or reverse the progression of this neurodegenerative disease. Regardless of the tremendous effort that the scientific field has done to find effective treatments for AD, promising candidates fail when tested in AD patients (Cummings et al., 2007; Raschetti et al., 2007; Exance, 2010; van Dyck, 2018). Most of the recent clinical trials that attempt treating AD focus on inhibiting the main known culprits of AD. The central targets are amyloid production and aggregation, largely A β by immune therapy and pharmacological enzyme inhibition (BACE inhibitors); the use of NSAIDs to reduce inflammation; and even stem cell therapy to fight against neurodegeneration. However, all these attempts have failed probably because the therapeutic intervention was done in an

already very advanced pathology or because the treatment is directed to the wrong target (Mehta et al., 2017). It could also well be that the proposed approach is targeting only one of the players of this multifactorial disease. Therefore, an alternative strategy to fight against AD could be the prevention of the known modifiable risk factors and related mechanisms for the disease. This includes proper management of comorbidities associated such as vascular diseases (hypertension, CVD, stroke, ischemia), diabetes, epilepsy, brain injuries, and depression as well as modification of lifestyle and avoidance of deleterious habits. Here, we have reviewed many of them including: physical activity, sleep, diet, and use of tobacco and alcohol, and how by different mechanisms, these factors are able to reduce amyloid deposition and ameliorate cognitive impairment. Recent studies have estimated that intervention of several modifiable risk factors could prevent up to 35% of dementia cases (Livingston et al., 2017). Management of diet, exercise, and vascular risk in at-risk elderly population can, in fact, prevent cognitive functioning deterioration (Kivipelto et al., 2013; Ngandu et al., 2015; Soininen et al., 2017). However, some reports suggest that changes in these habits should be done early in life since modifying later life lifestyle factors may not decrease the conversion of MCI to AD dementia (Reijs et al., 2017) although it may ameliorate the course of the disease. Most of the studies compiled in this review evaluate the effect of risk factors when the AD-associated pathological changes are already present, but very few analyze the potential of those factors in preventing the onset of the disease, rather than the further development. Furthermore, most of the risk factors analyzed here can be considered both the cause and effect of AD. If they are a cause or risk factor, preclinical intervention may prevent the onset and development of AD, but if these factors are in fact an effect or a symptom, their treatment will still slow down the progression of the disease. Hence intervention of potential risks is highly recommended for either prevention or even amelioration of clinical symptoms of AD since most of these actions will also benefit general health status. Therefore, and while an effective treatment(s) is developed to treat AD, the most reasonable approach is to prevent AD onset by managing multiple risk factors way before any clinical symptom is observed.

AUTHOR CONTRIBUTIONS

GED, NG, GEs and OC drafted the article. IM-G provided a critical revision and generated the last version of the manuscript.

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Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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