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Review

Prevention of dementia in an ageing world: Evidence and biological rationale

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ABSTRACT

As the population ages, the number of people with dementia is expected to increase in the coming decades, with consequences at the societal and individual levels. In this narrative review, we provide a summary of the scientific evidence concerning dementia prevention, with a focus on the following three strategies: 1) Targeting the body to protect the brain, including prevention and treatment of cardiovascular morbidity; 2) Compensatory interventions to counteract brain ageing, including education and life-long engagement in cognitively and socially stimulating activities; and 3) Lifespan health promotion, such as a physically active lifestyle, smoking cessation, and a healthy and balanced diet. Next, we consider the biological mechanisms by which these strategies may act by taking into account the main pathways implicated in the development and progression of dementia: neurodegeneration, brain resilience, vascular damage, neuroinflammation, and oxidative stress. Based on the current evidence, and in line with the declining trends of dementia incidence in high-income countries, we conclude that timely multidomain preventive actions are promising strategies to reduce the dementia epidemic worldwide. There is still a considerable gap between the epidemiological evidence and its underlying biological mechanisms. Filling this gap will be crucial to move forward in dementia prevention worldwide.

1. Introduction

The world's population is ageing considerably due to declining fertility rates and increasing life expectancy. To this end, two billion people are expected to be older than 65 years by 2050 (World Report on Ageing and Health, World Health Organization [WHO], 2015. A longer life brings opportunities for individuals and society, since it enables people to pursue new activities and further contribute to the community. However, to a certain extent these positive attainments are contrasted by the progressive deterioration of older adults' physical and mental health and consequent need for increased medical and social care (Santoni et al., 2017).

Health in ageing is a multifaceted and complex phenomenon that results from a constant interaction between genetic background and environmental factors, rendering older people an extremely heterogeneous group (Calderon-Larranaga et al., 2019; Santoni et al., 2017). In spite of this heterogeneity, after age 70–75 all older adults will experience a rapid increase of morbidity and multimorbidity (co-occurrence of multiple age-related chronic disorders), especially cardiovascular and neuropsychiatric multimorbidity (Calderon-Larranaga et al., 2017). Among those, dementing disorders are the major cause of disability and dependency among older adults (Vetrano et al., 2018, 2019). Dementia is the fifth largest contributor to the global burden of disease, with an annual global economic cost that surpassed 1 trillion USD in 2018 (Collaborators, 2019; Winblad et al., 1999). The WHO and Alzheimer's Disease International (ADI) consider dementia a global public health priority (WHO and ADI, 2015: Dementia: a public health priority). In 2018, nearly 50 million people were affected by Alzheimer's disease (AD) and other dementias worldwide, and this number is projected to double approximately every 20 years.

Decades of research in the field of dementia epidemiology have led to several achievements in the understanding of dementia's pathophysiology and etiology. First, ageing and the development of dementia are closely-related processes, and older age remains the strongest risk factor for dementia (Hou et al., 2019). In this regard, up to 70 % of individuals with dementia are older than 75 years (Vermunt et al., 2019). At the same time, dementia is not an inevitable consequence of ageing, and numerous studies have shown that several other factors are at play in its development and clinical features (Qiu and Fratiglioni, 2018). Second, in spite of many genetic and environmental determinants, a number of protective factors over the lifespan have been shown to counteract dementia onset and progression, acting via compensatory mechanisms

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(Dekhtyar et al., 2019; Wang et al., 2019; Whalley et al., 2006). Finally, neuropathological and neuroimaging studies have shown that neurodegeneration often coexists with cerebrovascular lesions in the majority of the dementia cases, particularly in the oldest-old (Qiu and Fratiglioni, 2015).

Over the past four decades, numerous clinical trials have failed to identify any drugs that could cure dementia or AD, or even substantially modify the disease process (Cummings et al., 2019; Panza et al., 2019; Sevigny et al., 2016). In contrast, a large body of evidence from epidemiological and simulation studies has suggested that interventions targeting major modifiable risk and protective factors are likely to delay or even halt the onset of clinical AD and dementia (Livingston et al., 2017; Norton et al., 2014). In this narrative review, we will focus primarily on overall dementia aiming to: (1) critically analyze the current knowledge on preventive strategies for dementia by summarizing the epidemiological evidence from observational and interventional studies; and (2) discuss the biological and neuropathological mechanisms that underlie this evidence.

2. Major preventive strategies: epidemiological evidence

Current epidemiological evidence points to three major strategies that may prevent or delay the onset of dementia. Major findings supporting these strategies are summarized below with special emphasis on the most recent reports.

2.1. Body-mind connection: targeting the body to protect the brain

Accumulating evidence indicates a close interplay between body and mind in the development of dementia (Grande et al., 2019, 2020). Cardiovascular diseases (CVDs) and dementia are highly prevalent in older adults, tend to aggregate in the same person, and share common risk factors such as hypertension, obesity, smoking, and dyslipidemia (Qiu and Fratiglioni, 2015; Qiu et al., 2020). The heart-brain connection is corroborated by the fact that the brain is a highly vascularized organ, despite comprising less than 3% of body weight. Therefore, the brain is particularly vulnerable to impairment in blood flow and vascular pathology. This puts people with heart diseases at high risk of developing dementia, and with a poorer prognosis (Qiu and Fratiglioni, 2015).

At the same time, a growing body of evidence supports a pivotal role for systemic atherosclerosis in cognitive deterioration in the ageing process, suggesting that even subclinical atherosclerotic pathology might be associated with poor vascular and brain health. *Post-mortem* data from the Baltimore Longitudinal Study on Aging showed that intracranial atherosclerosis increased the odds of dementia, independent of AD pathology and cerebral infarcts (Dolan et al., 2010). The etiologic role of atherosclerosis in AD is still controversial, but several population-based studies (e.g., the Rotterdam study) found correlations between carotid atherosclerosis and AD (Hofman et al., 1997; Yan et al., 2016). Notably, all but one of ten studies included in a systematic review linked asymptomatic carotid stenosis to cognitive dysfunction, suggesting that subclinical changes are at play in cognitive deterioration in the presence of atherosclerosis (Chang et al., 2013).

Atrial fibrillation (AF), ischemic heart disease, and heart failure have been the most well-characterized and most often studied heart diseases involved in the development of dementia. In a recent meta-analysis of cohort studies, the presence of coronary heart disease and heart failure was associated with a 27 % and 60 % increased risk of dementia, respectively (Wolters et al., 2018. A population-based Swedish cohort including 2685 dementia-free participants detected a steeper cognitive decline and a greater risk of dementia in people suffering from AF than in those free from this condition Ding et al., 2018). Among AF participants, the use of anticoagulants was associated with a 40–60 % decreased risk of dementia (Kim et al., 2019; Saglietto et al., 2019), which is in line with the current guidelines that recommend the use of anticoagulants as the first line treatment in patients with AF. Interestingly, several studies have demonstrated a greater risk of dementia in people with AF even after excluding incident strokes, adding weight to the idea that other biological mechanisms are at play in the brain damage due to AF, including silent brain infarction (Vermeer et al., 2007) and systemic inflammation (Harada et al., 2015).

Stroke itself doubles the risk of developing dementia (Hachinski et al., 2019, 2018; Pendlebury and Rothwell, 2009) and could accelerate its onset by as much as 10 years (De Ronchi et al., 2007; Knopman and Hooshmand, 2017). In a recent longitudinal population-based study including residents of Oxfordshire, UK, the 1-year incidence of post-stroke dementia was 34.3 % in patients with severe stroke (NIHSS $>$ 10), 8.2 % in patients with minor stroke (NIHSS $<$ 3) and 5.2 % in those with transient ischemic attack (Pendlebury and Rothwell, 2009). This highlights the importance of the clinical features of stroke, such as the subtype, severity, and location, as well as the importance of the individuals' demographic characteristics, such as pre-existing vascular risk factors, cerebral microvascular burden (e.g., white matter diseases), comorbidities, educational attainment, and basal cognitive function (Palmer et al., 2019).

Midlife hypertension and obesity are established risk factors for the development of dementia later in life, accounting for 5% of all AD cases worldwide (Norton et al., 2014). In contrast, among very old people (e.g., $\geq$75 years), low blood pressure/hypotension and underweight/weight loss have been linked to an increased dementia risk. Such an age-dependent relationship between certain cardiometabolic risk factors and risk of dementia entails that a life-course approach is essential to understand the specific risk profiles for dementia. In the Finnish CAIDE study, midlife high systolic blood pressure nearly doubled the risk of late-life AD (Kivipelto et al., 2005), and, notably, midlife obesity, hypertension, and high cholesterol levels tended to cluster together and to further increase the likelihood of dementia. A recent meta-analysis of prospective cohort studies with median follow-ups across cohorts of 7–22 years showed that, among people with high blood pressure, the use of antihypertensive medications was associated with a reduced risk of developing dementia (HR 0.88, 95 % CI 0.79–0.98) and AD (HR 0.84, 95 % CI: 0.73–0.97) compared with those not using those medications (Ding et al., 2019). No evidence was found for specific drug class in reducing such a risk. Despite these findings from observational studies, results from RCTs have been inconclusive. Differences in the target populations, length of follow-up, molecules, and indication bias might have led to such discrepancy. Interestingly, recent results from the Systolic Blood Pressure Intervention Trial-Memory and Cognition in Decreased Hypertension (SPRINT-MIND) study have shown that the incidence of dementia was collectively lower, although not statistically significant, with intensive treatment over standard treatment (The SPRINT MIND Investigators for the SPRINT Research Group et al., 2019). Such potential beneficial effect is promising, but the impact of optimal blood pressure control, especially in the older-old groups (i.e. 80+ years) is still unclear (Peters et al., 2019).

Finally, similar to hypertension and hypercholesterolemia, the association between body mass index (BMI) and dementia is closely age-dependent. Underweight and weight loss later in life anticipate subsequent risk of dementia, but they may reflect early clinical markers of the disease rather than risk factors for dementia.

Systematic reviews have shown that diabetes in mid- and late-life is associated with both AD and vascular dementia (Biessels et al., 2006; Xue et al., 2019. Further, in a Swedish study including 2746 older adults, pre-diabetes and diabetes were independently associated not only with accelerated cognitive decline but also with faster white matter hyperintensities accumulation Marseglia et al., 2019a).

2.2. Interventions to counteract brain ageing

The age-related cognitive consequences of accumulating cellular damage to the brain and progressive neuronal loss can be counteracted

by life-long engagement in activities that enhance compensatory mechanisms to delay the onset of dementia. Comprehensive reviews have been recently published on this topic; here we summarize the main findings (Qiu and Fratiglioni, 2018; Fratiglioni et al., 2020).

Higher levels of education can be considered a proxy for lifelong cognitive enhancing activity, which may maintain cognitive function until later in life and even delay the onset of dementia (Berggren et al., 2018; Larsson et al., 2017). Several studies have demonstrated that education increases the basal level of cognition, with no further effect on the rate of cognitive decline during ageing (Nyberg et al., 2012; Sharp and Gatz, 2011). However, older adults with higher cognitive levels will reach the threshold to express dementia symptoms later than counterparts with lower initial cognitive levels. Finally, a dose-response meta-analysis of prospective cohort studies has shown that education reduces dementia risk in a dose-dependent manner, with a 7% risk reduction per year increase in schooling (Xu et al., 2016). However, it is still unclear whether education after secondary school confers additional protective effects (Livingston et al., 2017).

The role of education in dementia development must be considered in the context of a life-course model, since early-life education affects a number of closely interconnected factors, including lifestyle and occupation. Epidemiological studies have related psychosocial working conditions to late-life cognition. Passive jobs (low demands and low control) entail lack of motivation and mental stimulation and may be detrimental for learning capacity and cognitive performance. Similarly, a stressful work scenario can affect the brain and cognition through greater release of stress hormones and indirect increase of CVDs (Sindi et al., 2017). Thus, workplace conditions are increasingly recognized as a factor of extreme importance in the development of dementia and need to be considered alongside other psychosocial and lifestyle factors (Pan et al., 2019a, b)

Late life seems to be a crucial period in conferring protective effects against dementia as well. Evidence linking rich social network with reduced dementia risk emerged more than two decades ago (Fratiglioni et al., 2004, 2000). Since then, several original studies and meta-analyses have demonstrated the beneficial effects of social contact and social engagement for dementia risk reduction (Bennett et al., 2014, 2006; Fratiglioni and Wang, 2007). One caveat in these studies is reverse causality: dementia could lead to social isolation and social withdrawal because prodromal and subclinical signs and symptoms of dementia may be present even a decade before its onset. Some studies have attempted to address this issue by excluding incident dementia cases early in the observational period, but longitudinal studies with longer follow-ups are still highly recommended. Similarly, late-life leisure activities involving mental, physical and social domains have been indicated as crucial contributors to brain protection (Grande et al., 2014, 2018).

As psychosocial and lifestyle factors tend to be closely connected, recent studies have adopted an integrated approach taking into account the whole lifespan. The main conclusion from these studies is that it is never too late to start interventions aimed at enhancing compensatory factors to counteract brain ageing (Wang et al., 2017a, 2019). Interestingly, some studies investigating the interplay of psychosocial and lifestyle factors with genetic factors and health conditions with regards to dementia risk have led to promising results. For instance, in the Swedish National Study on Aging and Care in Kungsholmen (SNAC-K), lifelong participation in reserve-enriching activities (early life education, midlife work complexity, late life leisure activities and social networks) seems to attenuate the risk of dementia even in the presence of a major genetic risk factor, APOE ε4 alleles (Dekhtyar et al., 2019). Findings from the SNAC-K study have also shown that participation in mentally, socially, and physically stimulating activities can minimize the detrimental effect of diabetes on brain ageing – that is, cognitive decline, dementia risk, and brain atrophy (Marseglia et al., 2019b).

2.3. Lifespan health promotion to reduce dementia risk

A healthy lifestyle over the whole lifespan has shown to considerably reduce the risk of dementia later in life (Winblad et al., 2016). Evidence from longitudinal observational studies has accumulated during the past decades and has shown that several potentially modifiable factors acting in mid-life are linked to late life dementia. Studies investigating the same factors later in life are more challenging to interpret: any association between late-life factors and the risk of dementia might reflect the consequences of the disease process because these factors or behaviours might be affected by the underlying AD pathology even in the preclinical phase. Thus, the issue of reverse causality is particularly relevant in a disease like dementia, which is characterized by a long pre-symptomatic period.

First, several studies suggest that sedentary behaviours increase psychological stress and are associated with greater vascular and metabolic burden due to a disrupted homeostasis in blood pressure and glycaemic levels (Panahi and Tremblay, 2018). The WHO guidelines on risk reduction for cognitive decline and dementia concluded that physical activity should be recommended to adults with normal cognition to reduce the risk of cognitive decline (WHO, 2019). The beneficial effect on cognition is stronger for aerobic versus resistance training and is more convincing for cognitively intact individuals than for people with mild cognitive impairment. Interestingly, data from the Whitehall II study of the middle-aged cohort with a mean follow-up of 27 years did not support the neuroprotective effect of physical activity. This implies that the findings from relatively short-term longitudinal studies of a lower risk of dementia in physically active people may be attributable to reverse causation (Sabia et al., 2017).

Second, use of tobacco is the major risk factor not only for cancer and CVDs but also for dementia. Considering the global prevalence of smokers (around 30 %), about 14 % (around 4.7 million) of all AD cases worldwide are attributable to smoking (Norton et al., 2014). Evidence regarding the harmful effects of smoking on cognition is strong and shows a dose-response effect.

Third, excessive and long-term alcohol consumption has been associated with neurological conditions, such as alcoholic dementia and Wernicke-Korsakoff syndrome (Frankenburg, 2008). Even milder forms of cognitive decline and dementia have been attributed to alcohol abuse, which seems to cause neurotoxicity and neuroinflammation, but also affects the brain indirectly by promoting nutritional deficiency (thiamine) (Day et al., 2004). Conversely, light-to-moderate alcohol consumption is associated with a reduced risk of cardiovascular morbidity and cognitive decline and dementia, with respect to both alcohol abuse and a completely alcohol-free diet (Ruitenberg et al., 2002).

Finally, diet is an important factor that can modify the risk of subsequent cognitive impairment and dementia (Scarmeas et al., 2018, 2009). Emerging yet contrasting evidence, mainly from observational studies, has pointed to the protective effect of some nutrients, including omega-3 polyunsaturated fatty acids and vitamins such as the B complex (vitamins B6, B12 and folate), antioxidants (vitamin A, C and E) and vitamin D (Hooshmand et al., 2016). A regular intake of fish, fruits, vegetables, and potentially moderate alcohol and caffeine consumption has been demonstrated to have a protective effect on cognitive outcomes in older people. Research has recently focused on dietary patterns rather than single nutrients in their association with cognition, and suggests that adherence to healthy dietary patterns, such as the Mediterranean diet, is associated with a lower dementia risk (Prinelli et al., 2019a, b; Shakersain et al., 2016; Sindi et al., 2018). Multidomain interventions that also address nutrition might be promising for the prevention of cognitive dysfunction, but their results remain conflicting (Andrieu et al., 2017; Ngandu et al., 2015). The Lipididiet trial investigated the effects of a multinutrient combination (Fortasyn Connect, containing docosahexaenoic acid [DHA], eicosapentaenoic acid [EPA], uridine monophosphate, choline, vitamins B12, B6, C, E, and folic acid, phospholipids, and selenium) on cognition in prodromal

Alzheimer's disease and resulted in no change in cognition, as measured with a neuropsychological battery. This may be partially due to limited power (Soininen et al., 2017). Interestingly, a handful of randomized trials on the Mediterranean (Scarmeas et al., 2006) and the blood pressure lowering DASH diets (Dietary Approach to Systolic Hypertension) have demonstrated protective effect on cognition (Sacks et al., 1999). In line with this evidence, the so-called Mediterranean-DASH diet intervention for neurodegenerative delay (MIND diet) was derived from the Mediterranean and DASH diet with some modifications based on the findings related to cognitive outcomes (van den Brink et al., 2019). For example, a number of prospective studies observed a slower rate of cognitive decline in people consuming high proportion of vegetables and fruits. In a longitudinal study including 960 participants of the Memory and Aging Project, the MIND diet was associated with a slower cognitive decline over time (Morris et al., 2015).

3. Biological rationale of the three suggested prevention actions

The risk and protective factors for dementia discussed above are intimately interconnected and may interact with an individual's genetic background to determine their risk for dementia development (Mattson, 2004).

The exact biological mechanisms by which these factors may affect the brain remain largely unknown and it is only recently that cohort studies with very long observational periods have emerged to fill the knowledge gap between the epidemiological evidence and its biological basis.

Table 1 summarizes the current knowledge concerning the biological mechanisms underlying the aforementioned preventive actions.

3.1. Neurodegeneration

The pathological hallmarks of AD are the extracellular deposition of amyloid-β (plaques) and the intracellular accumulation of hyperphosphorylated tau (p-tau) protein (neurofibrillary tangles) (Mattson, 2004). Those two features have been considered the toxic events that lead to subsequent neurodegeneration in AD (Palmqvist et al., 2017). Neurodegeneration is characterized by synaptic dysfunction, increased neuronal vulnerability, and progressive neuronal loss (Hou et al., 2019; Mattson and Magnus, 2006). *In-vivo* it is detected by regional and global brain atrophy on structural brain MRI, brain hypomethabolism at FDG-PET and increased total tau levels in the CSF. However, the nature of the interaction between Aβ and tau in leading to neurodegeneration is still poorly understood and the link with neurodegeneration appears to be stronger for tau rather than for Aβ. This is further supported by additional observations. First, the topographical deposition of Aβ and tau seems to follow different patterns (Hanseeuw et al., 2019; Iaccarino et al., 2018; Pereira et al., 2016; Vemuri and Scholl, 2017); second, it is increasingly common to detect brain and hippocampal atrophy and FDG-PET hypometabolism (indirect signs of neurodegeneration) in the absence of Aβ and tau deposition (Jack et al., 2016). Interestingly, neurodegeneration is also associated with (micro)vascular dysfunction, neurovascular disintegration and leakage in the blood-brain barrier (BBB), which in turn alter the brain supply of energy and oxygen.

Evidence from neuroimaging and neuropathological studies has demonstrated that many, if not all, of the CVDs are associated with AD pathology, dysfunction in cerebral metabolism, and accelerated brain atrophy (Marseglia et al., 2019a; Wang et al., 2017b, 2018). The Atherosclerosis Risk in Communities (ARIC)–PET cohort study found that having more than two midlife vascular risk factors was associated with elevated amyloid deposition in the brain (61.2 % vs. 30.8 %). In a longitudinal study including 463 dementia-free participants, higher vascular risk in early adulthood was strongly associated with smaller whole-brain volumes and greater white matter–hyperintensities at age 70, but not with amyloid deposition (Lane et al., 2020).

The association between cardiometabolic conditions and neurodegeneration has huge clinical and public health implications, given that the vascular component of dementia remains the only one to be preventable and treatable so far. Furthermore, these results highlight the importance of extending our knowledge to sub-clinical measures concerning the subtle but continuous vascular damage that occurs throughout the lifespan.

3.2. Brain resilience

The heterogeneity in cognitive decline during ageing has led to the hypothesis that possible resilience mechanisms may be at play to counteract brain ageing and maintain cognitive performance. As Mattson et al. demonstrated (Mattson and Magnus, 2006), ageing affects neurobiological function at multiple levels (e.g. increased oxidative stress, perturbed energy homeostasis, accumulation of damaged proteins and lesions to nucleic acids). The accumulation of such damage is exacerbated in neurodegenerative disorders, which also exhibits

Table 1
Current evidence for preventive strategies, targeting risk and protective factors, and the underlying biological mechanisms.

Preventive strategies	Risk and protective factors	Biological mechanisms				
		Neurodegeneration	Brain resilience	Vascular damage	Inflammation	Oxidative stress
Targeting the body to protect the brain	Systemic and cerebral atherosclerosis	[c]		[a]	[a]	[c]
	Atrial fibrillation	[c]		[a]	[b]	[c]
	Heart failure	[c]		[a]	[b]	[c]
	Ischemic heart disease	[c]		[a]	[b]	[c]
	Mid-life hypertension	[b]		[a]	[b]	[c]
	Diabetes	[b]		[a]	[b]	[b]
	Mid-life obesity	[c]				
Interventions to counteract brain aging	High education		[b]			
	Work complexity		[b]			[c] (Reduced)
	Leisure-time mentally, socially and physically stimulating activities		[b]	[b] (Reduced)	[b] (Reduced)	[c] (Reduced)
Lifespan health promotion to reduce dementia risk	Physical inactivity	[b]	[b]	[a]	[b]	[c]
	Smoking	[c]		[a]	[b]	[c]
	Excessive alcohol consumption	[c]		[a]	[b]	[c]
	Unhealthy/imbalanced diet	[c]		[a]	[b]	[c]

[a] Strong evidence (i.e. evidence from meta-analyses, RCTs, well designed cohort studies with consistent findings).
[b] Emerging evidence (i.e. less consistent findings).
[c] Limited evidence (i.e. limited number of studies).

neuronal death, synaptic dysfunction and loss of white matter integrity.

Brain resilience can occur through several mechanisms such as cognitive reserve and brain maintenance (Cabeza et al., 2018; Fratiglioni et al., 2004; Fratiglioni and Wang, 2007; Stern et al., 2018). The concept of *cognitive reserve* involves the existence of structures and networks not "needed for immediate use but available if required" (Nyberg et al., 2012). This concept implies the presence of a threshold whereby the premorbid amount of brain structures and connections (namely the size, neuronal counts, synaptic density and networks) determines a person's capacity to cope with a certain degree of brain pathology (Chapko et al., 2018). Following this model, only when brain resources fall below a certain threshold will cognitive symptoms start to appear. As a consequence, reaching high brain reserve allows individuals to delay the onset of cognitive symptoms. To this end, several epidemiological studies have indeed shown that, for example, highly educated adults will reach the threshold of functional impairment (e.g. the diagnosis of dementia) at a later stage (Hall et al., 2009). In addition, neuroimaging studies demonstrated that among individuals with dementia and similar level of cognition, those who were highly educated had greater cerebral atrophy, greater parietotemporal perfusion deficit, and lower glucose metabolism in the posterior temporo-occipital association cortex. Being highly educated does not prevent neurodegeneration or vascular pathologies in the brain, but allows the brain to better cope with such damages.

Brain maintenance refers to the preservation and promotion of neurochemical, structural and functional brain integrity. An example is the evidence of recovery from post-stroke aphasia due to left hemisphere damage via recruitment of right hemisphere regions that usually do not support language processes in non-pathological brains (Cabeza, 2002). Twin studies indicate that individual differences in cognition are closely linked to genetic variability. Some genetic variants are implicated in the maintenance of higher levels of brain functioning. One example is brain-derived neurotrophic factor (BDNF), which plays an important role in learning and memory by regulating activity-dependent synaptic plasticity. In addition to genetic determinants and education attainment, environmental factors and lifestyle habits may also play a role in the maintenance of brain integrity and cognitive performance in old age. These findings suggest that the preservation of an active lifestyle throughout late life is implicated in the functional compensation for brain ageing.

3.3. Vascular damage

Besides the obvious vascular damage observed in vascular and post-stroke dementia, it has been shown that up to 80 % of patients with a clinical diagnosis of AD (and no evidence of mixed/vascular *in-vivo* component) have a large degree of vascular pathology in the brain at death, including lacunes, microbleeds, cortical and microinfarcts (Kisler et al., 2017; Toledo et al., 2013). Indeed, recent studies have demonstrated that vascular dysfunction appears in the first steps of the pathophysiological process leading to AD and dementia, and further contributes to neurodegeneration. Similarly, a breakdown in the BBB seems to happen particularly early in the hippocampus and correlates with cognitive symptoms (Montagne et al., 2015; Nation et al., 2019; Sweeney et al., 2019).

The close structural and functional connection between brain cells (both neurons and glia) and cerebral blood vessels, together with their interconnected reaction to brain injuries, supports the existence of a link between those structures, referred to as the "neurovascular unit" (Hachinski et al., 2019). Alterations of the neurovascular unit have been deemed a crucial joint mechanism for both stroke and dementia. Cerebral hypoperfusion and hypoxia, cerebral ischemia or microbleeds, and the release of natriuretic peptides in patients with AF, ischemic heart diseases, and heart failure are among the most common and plausible mechanisms that link such diseases to poor cognitive outcomes (Gartner et al., 2008). For instance, AF causes clinical and silent brain infarcts, and may reduce cerebral perfusion due to irregular heartbeat and reduced cardiac output (Ding et al., 2018; Ryden et al., 2019). Finally, it can trigger the release of inflammatory cytokines, causing platelet activation. Of note, recent studies have revealed that the association of AF with subsequent dementia is independent from clinical stroke (Saglietto et al., 2019), supporting the possibility of a separate and possibly direct pathway involved in the brain damage related to AF (Kim et al., 2019).

3.4. Inflammation

Neuroinflammation is a crucial component in the pathogenesis of dementia (Ardura-Fabregat et al., 2017). Individuals who died with AD have shown increased levels of inflammatory biomarkers in the brain, and epidemiological studies have linked the use of anti-inflammatory drugs to reduced dementia risk. Several *in-vitro* and animal studies have demonstrated that neuroinflammation could even trigger amyloid deposition, contributing to brain damage early in the disease process (Heneka et al., 2015). In accordance with this view, inflammation is seen as a driving force in the development of AD/dementia (Arranz and De Strooper, 2019). At the same time, neuroinflammation can be seen as an epiphenomenon of brain dysfunction and neuronal loss, further accelerated by plaques and tangles deposition, and thus represents a consequence of brain damage (Bowman et al., 2018). Many genetic loci associated with higher risk of dementia are expressed by glial cells involved in the inflammatory response in the CNS (De Strooper and Karran, 2016). For example, astrocytes are the main cells expressing APOE in the brain, and individuals with homozygous APOE ε4 have pericytes' degeneration and BBB damage – factors involved in the proinflammatory responses and neurodegeneration observed in AD (Liu et al., 2013).

Interestingly, a systemic imbalance between inflammatory and anti-inflammatory agents (a frequent finding in old individuals termed 'inflammaging') (Franceschi and Campisi, 2014; Franceschi et al., 2018) and several chronic diseases (heart and kidney failures, AF, diabetes), can also lead to a pro-inflammatory state that can in turn affect the brain (Giunta et al., 2008). According to geroscience, inflammation is one of the pillars of ageing that is involved in several age-related diseases, including dementia.

Finally, mounting evidence has shown that animals maintained on dietary restriction experienced lower level of systemic inflammation and lower levels of oxidative stress and DNA damage (Mattson, 2005). In laboratory animals, intermittent fasting extends the lifespan by up to 40 % and protects against major chronic diseases, including cancer, diabetes, and kidney disease. Recently, in mouse models, it has also been demonstrated that ketones may counteract AD pathogenesis by reducing the amyloidogenic enzymatic processing of APP, suppressing inflammation and up-regulating the adaptive neuronal stress-resistance pathways (Mattson, 2005).

3.5. Oxidative stress

Oxidative stress has been implicated in the pathogenesis and progression of AD and dementia (Martins et al., 2018). Patients with AD or dementia showed increased levels of ROS and RNS in the brain, particularly in brain regions that are rich in amyloid plaques or highly neurodegenerated. At the same time, increased oxidative damage and lipid peroxidation are observed in individuals with mild cognitive impairment. Such molecular damage accelerates glucose dysmetabolism and impairs $Ca2+$ homeostasis, further interfering with DNA transcription and RNA function with serious detrimental effects on the synthesis of essential proteins (Butterfield and Halliwell, 2019).

Diabetes has been strongly related to both increased oxidative stress and dementia. Indeed, the brain is an energy-demanding organ and it strongly relies on adenosine triphosphate (ATP) production via glycolysis, trycarboxylic acid (TCA) cycle and oxidative phosphorylation.

The reduced bioavailability of glucose together with the production of advanced glycation end-products (AGEs) that characterizes diabetes, renders people with diabetes prone to oxidative damages and their cognitive repercussions.

This crucial role of oxidative stress in the pathogenesis of dementia has led to the hypothesis that the inhibition of oxidative damage might have beneficial effects for cognitive function (Devore et al., 2010). It is therefore surprising that the results of clinical trials in people with mild cognitive impairment and AD involving antioxidant therapies (such as vitamin E) have been largely disappointing. Additionally, potential health risks have been reported with vitamin E supplementation. Therefore, no recommendation is given for supplementations with antioxidants in the prevention of dementia or AD (Masaki et al., 2000).

4. Concluding remarks

Despite the global ageing of the population, accumulating epidemiological evidence has demonstrated that the trend in dementia incidence is declining in high-income countries (Wu et al., 2017; Ding et al., 2020a,b). Considerable reductions in dementia risk can partially offset the growing number of older people. Such a reduction in dementia incidence reported in some European countries and North America could be partially related to the implementation of better preventive strategies and treatment of chronic cardiometabolic conditions (Khachaturian et al., 2019). Also, the promotion of activities that enhance compensatory mechanisms to counteract brain ageing and pathological burden, as well as the advancement in healthy lifestyles, are considered crucial interventions to reduce dementia risk (Sindi et al., 2015; Solomon et al., 2014).

The contribution of vascular risk factors to dementia is higher in low- and middle-income countries than in western societies because of the increasing incidence of vascular risk factors in these parts of the world (e.g. diabetes mellitus, smoking, metabolic syndrome, and hypertension) (Wu et al., 2016). Preventing stroke, treating heart diseases, and reducing vascular risk factor burden would therefore represent a powerful strategy to reduce the burden of dementia worldwide (Hachinski et al., 2019).

The findings from several epidemiological studies summarized in this narrative review highlight also another critical aspect in dementia prevention: all the preventive strategies, to be effective, need to be implemented in the framework of a life-course approach (Kivipelto et al., 2018). For example, the beneficial effect of the control of hypertension, obesity and other modifiable cardiometabolic risk factors results stronger when these factors are managed in midlife, compared to later life. Noteworthy, despite the fact that a lifelong perspective in dementia prevention is preferable, an important take-home message from the results of the studies carried out including older subgroups is that it is never too late to start prevention. Preventive interventions that improve the risk profile even of older individuals can delay the onset of dementia. To this end, multidomain interventions can be considered a proof of concept for such hypothesis, since they demonstrate that even a late-life multidimensional intervention can reduce the rate of cognitive decline and eventually postpone dementia onset. Three large multidomain trials have now been completed in Europe and include the Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER; NCT01041989), the French Multidomain Alzheimer Preventive Trial (MAPT; NCT00672685) and the Dutch Prevention of Dementia by Intensive Vascular Care (PreDIVA; ISRCTN29711771). The multidomain intervention is mainly based on improvement of lifestyle and adherence to medical treatments for vascular risk factors and vascular diseases. Although the FINGER trial showed evidence that multidomain interventions might slow the rate of cognitive decline among older adults at higher risk of dementia, the potential effects of multidomain interventions on reducing dementia risk remain to be demonstrated.

International programs and networks are pivotal to implement these strategies in diverse populations and settings. The World-Wide FINGERS stems from the experience of the FINGER that showed a beneficial effect on cognitive performance in people at high risk of dementia participating in a multidomain lifestyle intervention (including management of vascular and lifestyle-related risk factors for dementia) (Ngandu et al., 2015). Such multidomain intervention model will be tested in different populations and settings across the world, and some of the studies have already been launched in 2018. One key question that will be answered by this new generation of trials will be whether these preventive approaches will be sustainable and effective for population with different geographical, economic, and cultural settings.

Dementia is a complex disorder in which several molecular and cellular dysfunctions are at play. Thus, it is not surprising that several factors have been linked to an increased or decreased risk of dementia, and three main prevention actions have been already identified and well characterized. At the moment, there is still a considerable gap between the epidemiological evidence and an understanding of the underlying biological and molecular mechanisms. Filling this gap will be a key step to move forward in the prevention of dementia worldwide.

Contributorship

Conception or design of the work: GG, CQ, LF. Drafting the article: GG. Critical revision of the manuscript: CQ, LF. Final approval of the manuscript: all the authors. All the authors fulfill the ICMJE criteria for authorship.

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Declaration of Competing Interest

None.

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QUESTIONNAIRE

G3 (21)

Prevention of dementia in an ageing world Evidence and biological rationale

INSTRUCTIONS

- Read through the article and answer the multiple-choice questions provided below.
- **Some questions may have more than one correct answer;** in which case you must mark **all** the correct answers.

Question 1: Which of the following are **CORRECT** regarding the world's ageing population**?**

- **A:** Two billion people are expected to be older than 65 years by 2050
- **B:** A longer life brings opportunities for individuals and society, because it enables people to pursue new activities and further contribute to the community
- **C:** Due to progressive deterioration of older adults' physical and mental health a need for increased medical and social care is created
- **D:** It is due to declining fertility rates and increasing life expectancy

Question 2: Decades of research in the field of dementia epidemiology led to which of the following achievements in the understanding of dementia's pathophysiology and aetiology?

- **A:** Dementia is an inevitable consequence of ageing
- **B:** Older age remains the strongest risk factor for dementia
- **C:** Very few protective factors have been shown to counteract dementia onset and progression
- **D:** Numerous studies have shown that several other factors are at play in the development and clinical features of dementia
- **E:** Neuropathological and neuroimaging studies have shown that neurodegeneration often coexists with cerebrovascular lesions in the majority of the dementia cases, particularly in the oldest-old

Question 3: Which of the following are major strategies that can prevent or delay the onset of dementia?

- **A:** Body-mind connection
- **B:** Counteracting brain ageing
- **C:** Lifespan health promotion
- **D:** None of the above

Question 4: The Finnish CAIDE study highlighted which of the following as risk factors for the development of dementia?

- **A:** Late life obesity
- **B:** Midlife high systolic blood pressure
- **C:** Hypotension
- **D:** High cholesterol levels
- **E:** All of the above

Question 5: Is it **TRUE** that an extensive social network is not necessarily linked to a reduced risk of developing dementia?

- **A:** YES
- **B:** NO

Question 6: Adherence to healthy dietary patterns is associated with a lower dementia risk. Which diets did the article specifically refer to?

- **A:** DASH diet
- **B:** Flexitarian diet
- **C:** Keto diet
- **D:** Mediterranean diet
- **E:** Vegan diet

Question 7: Evidence from neuroimaging and neuropathological studies have demonstrated that many of the cardiovascular diseases (CVDs) are associated with which of the following?

- **A:** Alzheimer's disease (AD) pathology
- **B:** Dysfunction in cerebral metabolism
- **C:** Parkinsonism
- **D:** Accelerated brain atrophy

Question 8: Which of the following are **CORRECT** regarding the mechanisms of brain resilience?

- **A:** *Brain maintenance* involves the existence of structures and networks not "needed for immediate use, but available if required"
- **B:** *Cognitive reserve* refers to the preservation and promotion of neurochemical, structural and functional brain integrity
- **C:** According to the cognitive reserve model, cognitive symptoms will start to appear when brain resources fall below a certain threshold
- **D:** Some genetic variants are implicated in the maintenance of higher levels of brain functioning

Question 9: Complete the statement:

"In laboratory animals, intermittent fasting extends the lifespan by up to ……. % and protects against major chronic diseases, including cancer, diabetes, and kidney disease.**"**

- **A:** 20
- **B:** 40
- **C:** 60
- **D:** 80

Question 10: Is the following statement **TRUE** or **FALSE?**

"This crucial role of oxidative stress in the pathogenesis of dementia has led to the hypothesis that the inhibition of oxidative damage might have beneficial effects for cognitive function**."**

- **A:** TRUE
- **B:** FALSE

END

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ANSWER SHEET

G3 (21)

Prevention of dementia in an ageing world Evidence and biological rationale

	A	B	C	D	E		A	B	C	D	E
1						6					
2						7					
3						8					
4						9					
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