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Nutrition for the ageing brain: Towards evidence for an optimal diet

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ABSTRACT

As people age they become increasingly susceptible to chronic and extremely debilitating brain diseases. The precise cause of the neuronal degeneration underlying these disorders, and indeed normal brain ageing remains however elusive. Considering the limits of existing preventive methods, there is a desire to develop effective and safe strategies. Growing preclinical and clinical research in healthy individuals or at the early stage of cognitive decline has demonstrated the beneficial impact of nutrition on cognitive functions. The present review is the most recent in a series produced by the Nutrition and Mental Performance Task Force under the auspice of the International Life Sciences Institute Europe (ILSI Europe). The latest scientific advances specific to how dietary nutrients and non-nutrient may affect cognitive ageing are presented. Furthermore, several key points related to mechanisms contributing to brain ageing, pathological conditions affecting brain function, and brain biomarkers are also discussed. Overall, findings are inconsistent and fragmented and more research is warranted to determine the underlying mechanisms and to establish dose-response relationships for optimal brain maintenance in different

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population subgroups. Such approaches are likely to provide the necessary evidence to develop research portfolios that will inform about new dietary recommendations on how to prevent cognitive decline.

Contents

1. Introduction

The significant increase in average life expectancy is one of society's great achievements which has been associated with a shift in the leading causes of illnesses from infectious to non-communicable diseases. It is well known that the percentage of populations categorized as elderly (*e.g.* 65 years and older) will increase dramatically in almost every country in the next few decades. By 2060, the elderly population will be expected to grow from 17.4% to nearly 30% worldwide (European Comission and Eurostat, 2012). At the same time, there is a wealth of disparate data related to how nutrients, non-nutrient, food components and whole diets may impact on cognitive health and ageing. Numerous epidemiological studies indicate that long-term intake of a Mediterranean diet (emphasizing amongst others fruits, vegetables, and olive oil) correlates with better cognition in aged populations (Feart et al., 2010; Scarmeas et al., 2009; van de Rest et al., 2015). Mechanistic investigations *in vitro* and in animal models have demonstrated that anti-inflammatory compounds in plants stimulate neurogenesis and protect neurons from noxious insults. However, such studies could not be replicated in humans (Stangl and Thuret, 2009) and treatments with ibuprofen, or foods, such as turmeric, although decrease pro-inflammation biomarkers only rarely show any pro-cognition effects, at least in intervention trials (Lee et al., 2013; Townsend and Pratico, 2005). Due to the lack of highly sensitive cognitive test batteries and control for individual differences, diets and nutrients are not proven to robustly alleviate cognitive decline over short periods.

In the past 10 years, high-calorie/low-dietary fibre diets and risk and incidence of diet-related diseases (*i.e.* Type 2 Diabetes Mellitus (T2DM) or cardiovascular disease (CVD)) have been associated with age-related cognitive decline (Beydoun et al., 2008; Loef and Walach, 2013; Nepal et al., 2014; Whitmer et al., 2005). Available data on beneficial effects of several ingredients or nutrients (*e.g.* dietary fibre, low-glycaemic carbohydrates, resveratrol and docosahexaenoic acid (DHA)) suggest that their consumption may decrease glycaemic spikes or improve plasma cholesterol or triglycerides levels, thus having the potential to help prevent cognitive decline (Greenwood, 2003; Greenwood and Winocur, 2005).

Randomized placebo-controlled trials (RCTs) are the gold standard to confirm the effect of a nutritional intervention on cognitive decline, maintenance or improvement. However, such trials may be impossible to conduct for some nutrients, where subtle effects are predicted to add up over decades and may be significantly influenced by individual differences in the rate of cognitive decline.

Currently, there are no dietary recommendations or accepted health claims referring to age-related cognition on the foodstuffs marketed. It may be expedient to weigh evidence from pilot, cohort, case control and animal studies, and evaluate these together, rather than taking into account only RCTs. Some nutrients may exhibit stronger effects in conjunction with others, and thus, one aim of this review is to weigh effects of nutrients in isolation, such as DHA taken as fish oil supplements, *versus* combinations of particular bioactives such as found in the Mediterranean diet. Although the present review is mostly focused on the role of nutrients in cognitive decline, it also offers some insights about different aspects related to the process of ageing. Thus, it highlights important considerations about normal and pathological ageing and its measurement through the use of biomarkers of cognitive status, as well as metabolic conditions that are considered as risk factors for cognitive decline. Therefore, the main goal of the present review is to provide the most recent evidence from human observational and intervention trials along with key mechanistic studies in cell and animal models, on the current state of knowledge on nutrition and healthy brain ageing.

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2. Normal and pathological decline in cognitive function

Major aspects of human cognitive function are influenced by a variety of factors including genetics, lifestyle, nutrition, disease, trauma, medicines, as well as both normal and pathological ageing. The group led by Salthouse (2010) has compiled a convincing body of evidence demonstrating that notable age-related decline in cognitive function occurs in healthy individuals starting from the late 20s and continuing throughout the adult lifespan. Some headline conclusions from this research are that such decline occurs in all individuals, concerns a wide range of major aspects of cognitive function (*i.e.* not simply memory) and are marked in nature (*e.g.* up to 2 standard deviations). Such findings have now been widely replicated (Wesnes and Ward, 2001; Wesnes and Edgar, 2014) and an important message is that the same aspects of cognition which decline with ageing also decline (at a much greater rate) both in Mild Cognitive Impairment (MCI) and in the dementias (Wesnes and Lenderking, 2012). Despite this compelling evidence, there is little regulatory support for the development of medicines to treat such declines. It is proposed that this time-based deterioration to crucial aspects of mental ability in healthy individuals should receive the same aggressive treatments as other age-related declines (such as eyesight deterioration). Nevertheless, there was a temporary surge of interest in this area over 25 years ago when the National Institute of Mental Health (NIMH) workgroup defined operational criteria for age-associated memory impairment (Crook et al., 1986). Then, over the next few years a variety of drugs were evaluated to treat this condition with some limited success (*e.g.* phosphatidylserine) (Crook et al., 1991). Criticism from some quarters that the pharmaceutical industry was creating a new condition simply to sell drugs to treat something which occurs in most individuals (O'Brien, 1999) led the industry to move away from this area and concentrate on pathological declines such as MCI, Alzheimer's disease (AD) and other dementias (Wesnes and Ward, 2001). In fact, during the last 10 years the news for novel drugs to treat MCI and AD has been overwhelmingly negative. No novel treatment has been approved for treating AD, despite a massive worldwide research effort which has been overshadowed by the failure of over a hundred putative treatments (Becker et al., 2008; Cummings et al., 2014; Mullard, 2012). This has led the field to move its focus to prodromal and even preclinical stages of dementia, stimulated by diagnostic criteria designed in 2007 to capture earlier stages based on early episodic memory loss alongside with biomarker evidence of disease pathology (Dubois et al., 2007). These criteria have been further refined (Albert et al., 2011; Dubois et al., 2010) and the goal posts broadened considerably with operational research criteria for preclinical AD (Sperling et al., 2011). Preclinical AD is particularly relevant as the trials would involve cognitively healthy elderly populations. Regulatory authorities have become proactive. In fact, in a recent publication authored by the Food and Drug Administration (FDA) officials, the point was made that in preclinical AD trials, where functional impairment would be difficult to assess, it could be feasible to approve a drug through the FDA's accelerated approval pathway on the basis of assessment of cognitive function alone (Kozauer and Katz, 2013). Therefore, a regulatory avenue has been opened in addition to new clinical criteria, and large trials in preclinical AD are already underway.

3. Biomarkers of cognitive status

AD is a slowly progressive neurodegenerative disorder with duration of several decades (Jack et al., 2011) showing 3 different phases; one preclinical and asymptomatic, a second one when cognitive performance starts to decline, and the last phase characterized by the typical memory-dominant dementia syndrome, which impairs everyday activities and patient autonomy (McKhann et al., 2011). In neuropsychiatric tradition, AD could only be diagnosed in a clinical setting if dementia was present, but a paradigm shift towards a more biologically defined AD diagnosis has been observed in recent years. The new National Institute on Ageing-Alzheimer's Association (NIA-AA) guidelines conceptualize AD as a progressive disorder including all possible stages from pre-symptomatic to severely demented (Jack et al., 2011; McKhann, 2011). This way of thinking implies that tissue changes precede the onset of clinical signs by many years, and neuropathological lesions can be found in elderly individuals who presently do not have, and may not live long enough to ever suffer from cognitive impairment and associated disability (Giaccone et al., 2011).

During the past 30 years, a large body of evidence has been accumulated indicating that a cascade of events related to the faulty production, degradation and clearance of amyloid-β protein (Aβ) lie at the heart of AD pathogenesis. Upstream events within this cascade include the overproduction of the amyloid-β precursor protein (AβPP) caused by rare mutations in the AβPP, PSEN1 or PSEN2 genes, malfunctioning of Aβ-degrading proteases and impaired clearance as a result of ineffective active or passive transport mechanisms (Jack et al., 2011). The imbalance between production and clearance results in excessive amounts of Aβ, which are believed to trigger a sequence of subsequent, *i.e.* downstream, pathological changes such as loss of synapses and neurons, impaired glucose utilisation, oxidative damage, brain metabolic reduction, tau hyperphosphorylation and associated neurofibrillary tangle formation, Aβ deposition in plaques and eventually neurotransmitter changes and widespread neurodegeneration. This complex cascade of pathological events continues throughout the course of AD, leading to an accumulation of structural and functional cerebral damages causing the typical clinical feature of disease (Jack et al., 2011, 2010a,b).

The hope for disease modification as well as technological advances in biomarker discovery fuel the search for biological indicators of the AD pathophysiological process, which can be used to identify neurodegeneration independently of its clinical manifestations (Hampel et al., 2010). Ideally, such a biomarker, alone or in combination with other markers, would distinguish between individuals with and without AD pathology. Furthermore, pathophysiological markers may also offer the added benefit of directly assessing response to treatment options that target core processes of AD pathogenesis. However, biomarker evidence of treatment efficacy should not replace clinical evidence of patient benefit.

Currently available AD biomarkers can generally be grouped into two categories. The first category comprises markers that indicate the type of pathology present, including cerebrospinal fluid (CSF) levels of $A\beta_{1\text{-}42}$, total tau (tTau) and phosphorylated tau $(pTau)_{181}$ (Blennow et al., 2010) and positron emission tomography (PET) tracers of fibrillar amyloid such as flutemetamol, florbetapir, florbetaben and Pittsburgh Compound B (Herholz and Ebmeier, 2011). The second category consists of markers that provide information on the topography of pathological changes, such as MRI and fluorodeoxyglucose PET (Dubois et al., 2010). Published evidence consistently shows that these biomarkers, alone or in combination with psychometric test results, offer an added value for the diagnosis of the early clinical stages of AD. Novel biomarkers that are more closely related to the core pathophysiological processes of AD are currently in development (Perneczky et al., 2014) such as soluble forms of APP, which can be measured in CSF (Perneczky et al., 2011) and blood (Perneczky et al., 2013).

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4. Metabolic and molecular mechanisms contributing to brain ageing

4.1. Cardiometabolic risk factors

The role of cardiometabolic health, including vascular stiffness and reactivity in cognitive health and decline are being increasingly recognized. In a 1-year longitudinal study in patients older than 80 years higher aortic stiffness was associated with more pronounced decline in cognitive function (Benetos et al., 2012), and microvascular function was significantly impaired in dementia patients as compared to controls (Khalil et al., 2007). Although, the line between normal and pathological ageing may not be well-defined, certain metabolic alterations such as obesity or Type 2 diabetes mellitus (T2DM) may account for an increased risk of suffering age-related cognitive decline, especially in the elderly. The dramatic global increase in the incidence of obesity over the last 50 years is having a large effect on the incidence of many chronic diseases including T2DM and dementia. Indeed, more than half (52%) of the adult population in the 27 European Union (EU) member states are overweight (BMI = 25.0–29.9 kg/m^2) or obese (BMI $\geq$ 30.0 kg/m^2) (Eurostat statistics database et al., 2012) with an average EU obesity incidence of 17% in adults (Eurostat statistics database et al., 2012). An excess of adipose tissue and its associated co-morbidities in middle-age, has emerged as a significant risk factor for age-related cognitive decline. A 27-year US cohort which consisted of overweight and obese individuals (aged 40–45 years) showed an odds-ratio (OR) 95% confidence interval (CI) of dementia of 1.35 (1.14–1.60) and 1.74 (1.34–2.26), respectively, relative to normal weight individuals (Whitmer et al., 2005). Comparable effect sizes of 1.5–2.0 OR have been documented in more recent analyses, including a *meta*-analysis, which reported an attributed risk of 12% of total dementia and 21% of AD associated with obesity in a US population (Beydoun et al., 2008). Indeed, including midlife obesity in forecast models typically results in a 10–20% higher prevalence of dementia (Loef and Walach, 2013; Nepal et al., 2014) than the doubling of prevalence predicted by 2030 based only on ageing-related demographics (Alzheimer's Disease International, 2009).

Metabolic syndrome (MetS) and T2DM have comparable impacts on dementia risk and have been reported in overweight and obese individuals, respectively. For example, a relative risk of 1.20 (1.02–1.41; 95% CI) of cognitive impairment was evident in MetS subjects as compared to healthy controls (Yaffe et al., 2004). Furthermore, in a recent *meta*-analysis including 19 studies, subjects with diabetes presented higher risk for AD (relative risk (RR):1.46, 95% confidence interval (CI): 1.20–1.77), vascular dementia (RR: 2.48, 95% CI: 2.08–2.96), any dementia (RR: 1.51, 95% CI: 1.31–1.74) and MCI (RR: 1.21, 95% CI: 1.02–1.45) than those without (Cheng et al., 2012). Interestingly, these results also showed that diabetes increases the risk for AD independently of *APOE4* status, although subjects with both diabetes and *APOE4* had the highest risk for AD (Cheng et al., 2012).

A growing body of epidemiological evidence is also suggesting that metabolic syndrome (MetS) and its associated components (impaired glucose tolerance, abdominal or central obesity, hypertension, hypertriglyceridemia, and reduced high-density lipoprotein cholesterol) may be important in the development of age-related cognitive decline, mild cognitive impairment, vascular dementia, and AD (Frisardi et al., 2010; Panza et al., 2012b). Although some understanding exists regarding the role of glucose and insulin within the central nervous system (CNS), the physiological and molecular basis of the contribution of obesity and its comorbidities to cognitive decline, along with causality and independence of associations are poorly understood (Freeman et al., 2014), but are likely to include: a) impaired vascular function and brain perfusion (Benetos et al., 2012; Elias et al., 2009; Khalil et al., 2007; Picano et al., 2014), b) low grade inflammation, including altered adipose tissue production of adipokines (Kiliaan et al., 2014; Song and Lee, 2013), c) poor glucose tolerance and utilisation (Lamport et al., 2009), and d) loss of insulin sensitivity independent of the impact on glucose metabolism (Calvo-Ochoa and Arias, 2015; De Felice, 2013; Park et al., 2000; Williamson et al., 2012). In this context, AD is currently proposed as an "insulin resistant brain state" (Craft et al., 2013). In addition, insulin in the CNS is largely derived from the periphery (pancreas) with some local insulin produced by the *dentate gyrus* (hippocampus) and olfactory system (Kuwabara et al., 2011). In neurons, insulin regulates energy metabolism, differentiation, growth, survival, synaptic plasticity and neurotransmission and promotes hippocampal long-term potentiation (LTP), learning and memory (Bingham et al., 2002; Calvo-Ochoa and Arias, 2015; Kuwabara et al., 2011; Skeberdis et al., 2001). Therefore, a loss of insulin sensitivity would be predicted to negatively impact on these metabolic processes.

Neuroinflammation has been associated with the risk of developing dementia and cognitive decline (McGeer and McGeer, 1999; Yaffe et al., 2003). In a longitudinal study, Yaffe and colleagues examined the association between MetS and cognitive change in elderly Latinos. Participants with MetS with high inflammation (median serum CRP level $\geq$3.2 mg/L) had significantly reduces cognitive function, measured by using the Modified Mini-Mental State Examination (3MS) than those without high inflammation. In this study, the individual components of MetS were also examined as predictors of cognitive change. The authors concluded that, in elderly Latinos, the composite measure of metabolic syndrome is a greater risk for cognitive decline than its individual components, with the possible exception of impaired glucose control and high blood pressure (Yaffe et al., 2007).

Interestingly, Solfrizzi and colleagues concluded in a longitudinal Italian population-based sample, that MetS appeared to be a risk factor of progression to dementia in MCI patients. However, it is unknown how MetS could increase the risk of dementia in these patients (Solfrizzi et al., 2011). Unfortunately, in this study, the number of events of progression to dementia in MCI patients was not sufficient to allow the authors to analyse the effect of MetS on the risk of developing a subtype of dementia.

4.2. Anaemia

The role of anaemia on cognition is still controversial and the potential mechanisms by which anaemia could impact on cognitive decline are still not understood (Andro et al., 2013). The main hypothesis proposed, points to the role of the chronic low oxygenation of the aerobic cortical tissue, even more in the presence of compromised compensatory processes due to the neurodegenerative or vascular pathology underlying MCI (Andro et al., 2013). Alternatively, anaemia has been suggested as a frequent complication of chronic kidney disease which leads to decreased erythropoietin levels that in turn may increase the risk of neurodegeneration (Andro et al., 2013).

The number of studies investigating the relationship between anaemia or haemoglobin concentration and dementia or cognitive decline has increased in recent years. However, the results of these studies are inconsistent (Lucca et al., 2008). Conflicting results have been found in studies investigating the association between anaemia or haemoglobin concentration and dementia or AD or vascular dementia mainly due to not appropriately adjusted confounding factors or inaccurate methodology (Lucca et al., 2008). Consequently, larger size, prospective, more representative and methodologically robust studies are needed to establish the possible effect of mild anaemia on cognition in elderly persons.

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4.3. Oxidative stress

The brain is a highly metabolically active tissue that relies on oxidative phosphorylation as a way for maintaining energy. The level of oxidative stress plays a pivotal role in brain functioning and growing evidence suggests a delicate balance between free radicals production and brain protection or damage (Chakrabarti et al., 2011). A moderate oxy-radical production by the mitochondria, reported as physiological level of oxidative stress, is known to up regulate the mitochondrial biogenesis program and brain antioxidant capacity, and to act in brain protection. By contrast, accumulation of oxidative damages is a key mechanism of the ageing process and a common feature of ageing brain. That, together with age-related mitochondria decay, causes alterations of cellular architecture within the brain, and raises the fact that uncontrolled free radical production is a major contributor to the loss of neuronal homeostasis and neurodegenerative diseases development (Wang et al., 2014).

4.4. Neuroinflammation

It has been observed in animal models of AD and Parkinson Disease, that systemic inflammation generates an exacerbated immune response in the CNS through the local innate immune system. Then, the priming pattern triggered by activated microglia, can be influenced not only by the sequence of neurodegeneration but also by the systemic inflammation or other secondary stimuli. Priming makes the microglia susceptible to a secondary inflammatory stimulus, which can then trigger an exaggerated inflammatory response (Perry and Holmes, 2014). Activated microglia has the capacity to synthesize a wide range of pro-inflammatory and anti-inflammatory cytokines and molecular mediators, which contribute to the systemic inflammatory *milieu* and to the progression of neurodegenerative disease (Perry, 2004; Perry et al., 2007). During neurodegenerative events, neural damage leads to a loss or down regulation of neural ligands that bind to inhibitory receptors on the microglia, resulting in a reduced microglia inhibition. Priming of macrophages has been widely studied *in vitro* following the exposure to IFN-ɣ and lipopolysaccharide (Schroder et al., 2006). Low doses of lipopolysaccharides are sufficient to trigger microglia activation and sickness behaviour in both humans and non-human primates (Brydon et al., 2008; Hannestad et al., 2012; Harrison et al., 2009).

Nevertheless, other molecules expressed in the injured brain such as the colony-stimulating factor-1 (CSF-1) (Chapoval et al., 1998) and C—C motif chemokine 2 (CCL2) (Bhattacharyya et al., 2002; Rankine et al., 2006) can also prime microglia. Activation of CSF-1 receptor (CSF-1R) by CSF-1 and IL-34 (Greter et al., 2012; Wang et al., 2012) drive microglia proliferation (Gomez-Nicola et al., 2013), which is significantly important since the primed state and the increased number of microglia both contribute to the exaggerated response observed in the brain in neurodegenerative disorders.

In addition, mutations in CSF-1R also lead to important white matter damages associated with progressive dementia but the disease onset and severity strongly depend on the mutation (Nicholson et al., 2013). The effects of the mutation on white matter region along with the fact that microglia remains more in white matter than in grey matter, suggest that microglia may have an important role in myelin or axonal homeostasis.

Ageing, as the main risk factor for AD development, occurs with a chronic, low-grade systemic upregulation of the proinflammatory T helper type 1 response and a relative decline in the anti-inflammatory T helper type 2 response (Franceschi et al., 2007). A study which examined brain samples from patients with mild or late-stage AD investigated the type of the inflammatory response (M1- or M2-like: CNS activated microglia corresponding to 'cytotoxic' and 'repair' subpopulations of macrophages in other organs) and tried to find serum markers that were associated with these two phenotypes (Sudduth et al., 2013). Noticeably, the M1-like state was associated with increased levels of CCL3 and the M2-like state with increased serum levels of IL-1 receptor antagonists.

It is well known that in the ageing population, an increasing number of individuals have more than one systemic disease (Barnett et al., 2012), which indicates that systemic inflammation has a relevant importance as a risk factor for AD. The group of Perry et al. has demonstrated that systemic inflammation and acute infections are associated with an enhanced rate of cognitive decline (Holmes et al., 2009) and increased symptoms of sickness in AD patients (Holmes et al., 2011).

Therefore, according to all these data, the monitoring and prompt treatment of systemic disease, inflammation and infection may delay neurodegenerative disease progression and improve quality of life (Perry and Holmes, 2014).

4.5. AMPK signalling and autophagy

Although, the precise neurobiological origin of dementia remains controversial, systems medicine approaches integrating recent advances in molecular technologies with computational methods are able to address this complexity and to identify key molecular hubs relevant for neurodegenerative dementia. These approaches, supported by the fast growing knowledge of human interactome, offer a platform to systematically explore not only the molecular complexity of a particular disease but also the molecular relationships among apparently distinct diseases. The group of Caberlotto et al. (Caberlotto et al., 2013) applied these novel systems biology approaches not only to clarify the molecular basis of AD, but also to characterize the molecular alterations of the subgroup of neurodegenerative disorders with the shared core symptom of dementia. By convergent analysis of multidimensional datasets, their study on AD revealed a major role of metabolism and, predominantly, of AMP-activated kinase (AMPK) as a central dis-regulated process in AD. AMPK is a core signalling pathway in cellular homeostasis and crucial regulator of energy metabolism. Through the examination of neurodegenerative dementias, they integrated not only the current knowledge on the specific diseases, but also the molecular targets of drugs for the treatment of dementia. This study underlined once more the role of AMPK signalling and autophagy, a self-degradative process that is important for balancing sources of energy in response to nutrient stress, as the molecular basis of neurodegenerative dementia (Caberlotto and Nguyen, 2014). Similar results were obtained from the integrative analysis of AD and T2DM, two multifactorial diseases of ageing with marked common pathophysiological features, which confirmed the autophagy pathway as the molecular mechanism altered in both diseases (Caberlotto and Nguyen, 2015).

5. Prevention of cognitive decline through nutritional and other lifestyle interventions

Preclinical and clinical studies provide valuable data regarding the effect of particular dietary patterns and/or specific nutrients on cognitive function. For example, deleterious dietary habits (overfeeding, high caloric/low dietary fibre diet or consumption of low antioxidant nutrients) and sedentary lifestyle, or emotional stress, have been reported as key environmental factors for oxidative stress and brain disorders (Martin et al., 2006; Mattson, 2012). Insulin resistance (IR) which is found in overweight, MetS, and T2DM individuals is one of the leading causes of oxidative

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stress. Given the negative effects of IR, inflammation and oxidative stress in brain, several dietary components, acting as antioxidant, anti-inflammatory and/or insulin action potentiating factors, could positively participate in a preventive nutritional strategy for healthy ageing of brain. It is therefore necessary to increase research on the benefits of nutrition and healthy eating habits in order to identify the best dietary recommendations in human population. These will enable the prevention or delay of diseases and disability and increase quality of life in the elderly (Roman-Viñas and Serra-Majem, 2014). Among existing dietary patterns, adherence to a Mediterranean diet is associated with less cognitive decline, dementia, or AD (Cao et al., 2015; van de Rest et al., 2015) and fits the notion of a healthy dietary pattern (Maillot et al., 2011). For example, a *meta*-analysis showed that greater adherence to a Mediterranean-style dietary pattern during older adulthood was associated with a lower risk of developing several different health outcomes such as CVD, neurodegenerative disorders, cancer and overall mortality (Sofi et al., 2010). In general, the Mediterranean diet is characterized by a high intake of vegetables, fruits, cereals, nuts and olive oil (as the principal source of added fat), a moderate intake of fish and alcohol (mostly wine), and a low intake of dairy products, red meat and meat products (Bach-Faig et al., 2011). Higher adherence to a Mediterranean-style diet was associated with higher intakes of several antioxidant nutrients, and other food bioactives such as polyphenols, which are present in fruits, vegetables, cereals and beverages such as wine, coffee and tea. Particularly, the role of coffee and caffeine consumption in later-life cognitive decline and dementia has been examined in a recent systematic reviewed by Panza and colleagues including 28 studies, which reported a potential correlation of moderate consumption of coffee or caffeine-rich beverages with a reduction in cognitive decline (Panza et al., 2015). Consistent with this, Santos and colleagues in their systematic review and *meta*-analysis of caffeine and cognitive impairment/decline conducted in nine cohort and two case control studies reported a nonsignificant relative risk (RR) of 0.98 [95% Confidence Interval (CI): 0.87–1.11], with moderate heterogeneity (Santos et al., 2010). Although, there was a lack of a linear dose-response relationship and an association was not found in all cognitive domains investigated, most of reviewed population-based studies pointed to a neuroprotective effect of coffee or caffeine consumption against cognitive impairment and neurodegenerative disorders, with a stronger effect among women than men (Arab et al., 2013; Liu et al., 2016; Panza et al., 2015; Santos et al., 2010).

On the other hand, contrasting findings also exist between alcohol consumption and reduced risk of age-related cognitive decline (Panza et al., 2012a). One recent *meta*-analysis from epidemiological longitudinal studies on older adults suggested that, light-to-moderate alcohol (usually wine) consumption was associated with a 38% reduced risk of incident overall dementia (Peters et al., 2008). In addition, another *meta*-analysis reviewed 15 prospective studies including older adults and revealed that light-to-moderate alcohol intake was correlated with a 25–28% reduction in risk of AD, vascular dementia, and overall dementia as compared to alcohol abstinence (Anstey et al., 2009). Finally, a more recent systematic review and *meta*-analysis, which reviewed 74 studies in older individuals, found that moderate intake of alcohol reduced cognitive impairment or dementia risk, whereas heavy drinking was associated with a trend toward a higher risk for cognitive impairment and dementia (Neafsey and Collins, 2011). Altogether these studies indicate that light to moderate alcohol consumption may protect against AD and dementia. However, the importance of drinking patterns and specific beverages remain unknown (Ilomaki et al., 2015).

5.1. Specific nutrient levels and age-related cognitive decline

Examination of biochemical indicators of diet in subject populations at high risk for dementia can serve to develop an evidence base for distinct nutritional requirements for the prevention of cognitive decline. In addition, comprehensive assessment of nutritional status beyond single or few nutrients can provide insight into the interactive features between nutrients that may be relevant to translational efforts. Thus, these "nutrient biomarker patterns" can be related to risk for pathological, structural and metabolic changes that precede cognitive decline and provide insight into mechanism.

One of the earliest structural changes in the brain that precedes cognitive decline is the accumulation of paraventricular and subcortical deep white matter hyperintensities (WMH). These WMH may indicate a breakdown of the blood-brain barrier *via* ischemic changes and demyelination of axons (Prins and Scheltens, 2015) and are a risk factor for cognitive decline. The CSF/plasma ratio of blood derived albumin is another indicator of BBB function. Here an increase in the CSF/plasma albumin ratio indicates BBB breakdown (Chen, 2011). The BBB impairment is prevalent in about 25% of autopsy confirmed AD cases and is associated with more rapid decline over time. Specific nutrient concentrations in the CSF appear to be influenced by BBB integrity and this loss of CNS concentration is associated with worse prognosis in AD cases (Bowman, 2012). Another study has demonstrated that BBB function is modifiable through vitamin therapies (Lehmann et al., 2003). Thus maintaining BBB health may be one target for nutritional therapies aimed at maintaining cognitive function. This area and underlying changes at the BBB that influence transport and concentration of nutrients in the brain remain an open area for research.

One report applied a data-driven approach to derive nutrient biomarker patterns (NBPs) in the Oregon Brain Ageing Study. The study included 104 subjects with a mean age of 87 years-old and free of dementia at baseline. Eight distinct NBPs were identified and examined in relation to domain specific cognitive function and MRI measures of brain ageing (Bowman et al., 2012). The results were remarkable in the sense that it appeared that some NBPs were associated with global cognition and others mapped more to certain cognitive faculties only. This would suggest that certain nutrient combinations operate on general mechanisms in the brain while others are more discrete. For example, two NBPs were associated with more favourable cognitive and MRI measures: one vitamin profile (high plasma B vitamins, antioxidants C, and E and vitamins D) and another high in plasma ω-3 fatty acids. The vitamin profile explained a significant portion of variance in global cognitive function and particularly, attention, visuospatial and executive functions. It was also associated with less total brain atrophy, a phenomenon that can be driven by Alzheimer's type pathology. The omega ω-3 pattern appeared more important to vascular aspects (WMH volume and executive functions known to be sensitive to WMH accumulation). A third pattern characterized by high *trans*-fat was associated with less favourable cognitive functions across several domains and more total brain atrophy. Memory function was best in those with higher plasma lutein and HDL cholesterol (Bowman et al., 2012). The NBPs altogether explained 17% of the total variation in global cognitive function and 37% of total variation in total brain volume. These data suggest that biochemical indicators of diet capture magnitudes of effect well beyond what we are accustomed to observing in nutrition research. One explanation is that the nutrient biomarker pattern analysis appreciates "synergistic" features, and another is that misclassification bias of nutritional exposure is reduced in comparison to more conventional methods subject measures of diet in older adults. In a longitudinal study of older adults at risk for dementia and followed over 4 years, plasma levels of the two long chain polyunsaturated fatty acids EPA and DHA were associated with less executive function decline and that

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relationship appeared to be mediated by WMH burden (Bowman et al., 2013). These studies suggest that nutrient biomarker pattern analysis is a fruitful strategy for studying nutrition, metabolism and dementia. What and how nutrients influence the neurobiology that contributes to age-related cognitive decline warrants much more research. Combining human induced pluripotent stem cells (iPS) cells biology, molecular and nutritional neuro-epidemiology and clinical trials is a way forward.

5.2. Nutritional assessment for disease prevention

The purpose of nutritional assessment is to well-characterize the dietary patterns of individuals, and to assess their exposure to nutrients and the hundreds of non-nutrients provided by the diet, for example phytochemicals, food additives, and food contaminants. Then, this information can provide scientific evidence for the role of dietary factors on human health and well-being. Other purposes of nutritional assessment are to identify population groups who do not have an adequate nutrition for disease prevention and to develop nutrition programs for at risk populations in order to monitor their impact. Nutritional assessment is still a huge challenge, due to the extraordinary heterogeneity and variability of food choices, and our limited knowledge of the composition of foods beyond the ~60 essential nutrients. Ideal methods of nutritional assessment should be accurate, sensitive and applicable to many populations. Currently, available methods fall into four categories: 1) anthropometric methods, 2) clinical examination, 3) questionnaires, and 4) biomarkers. Anthropometric methods such as body mass index (BMI) measurement have been considered as indicators of the adequacy of energy intake, but the correlation with diet quality is very questionable. Clinical examination has been used to diagnose severe vitamin or mineral deficiencies. However, this method is not appropriate for mild deficiencies. Today, dietary assessment is often conducted using Food Frequency Questionnaires (FFQs), where subjects must remember their intake of 10–300 food items over the previous year. Multiple 24 h recalls and food records are more precise but more expensive and therefore, other new technologies have been developed. Now, web-based questionnaires are applied in large cohort studies, as in the French NutriNet-Santé cohort which includes over 200,000 subjects (Hercberg et al., 2010). Smart phone applications also seem promising. Nevertheless, even with more technology, questionnaires have inherent limitations due to self-reporting (Maillot et al., 2011; Roman-Viñas and Serra-Majem, 2014; Sofi et al., 2010) and are susceptible to recall bias. Even if statistical techniques have been developed to correct measurement errors, questionnaires, especially FFQs, are suspected to markedly attenuate associations existing between dietary factors and health outcomes (Bach-Faig et al., 2011). The last approach for nutritional assessment is the use of biomarkers, which are quantified through targeted analyses of biofluids or tissues (Arts and Hollman, 2005; Scalbert et al., 2005). Biomarkers are independent of all the errors associated with questionnaires. Today, only a limited number of validated biomarkers of food intake have been use in epidemiology (Arts and Hollman, 2005; Scalbert et al., 2005), for example plasma vitamin C or carotenoids for fruit and vegetable intake, alkylresorcinols for whole grains, and urine methyl-histidine for meat. Some polyphenols have also been occasionally used as biomarkers of intake for their main dietary source (van Dam et al., 2013), for example resveratrol for red wine or hesperetin for orange (Cassidy et al., 2013). These biomarkers have been discovered using a hypothesis-driven approach which means that a specific compound of the food was previously known, its bioavailability was documented and then a reliable method of analysis could be developed. However, validated markers discovered with this approach do not cover the large diversity of food in the human diet, and many new biomarkers are still needed.

In the last decade, metabolomics has emerged as a data-driven approach for biomarker discovery. The concept of the food metabolome has been defined (Scalbert et al., 2014) which represents all the metabolites present in human tissues and biofluids that directly derive from the digestion and metabolism of food chemicals. The food metabolome is affected by both, the dietary habits and the metabolic capacity of individuals.As an example, a medium-term controlled intervention study was conducted to find biomarkers of citrus fruits intake (Pujos-Guillot et al., 2013) where 12 volunteers consumed 500 mL/day of orange juice or control drink for one month, in a cross-over design. The urine metabolomes analysed by non-targeted high resolution mass spectrometry were compared at the end of the experimental period. Some expected candidates biomarkers of orange juice intake were identified such as the glucuronides of the citrus flavanones, hesperetin and naringenin but new candidates were also found, including some terpene metabolites as well as proline betaine, which seemed even more sensitive than the flavanone metabolites (Pujos-Guillot et al., 2013). Proline betaine has been validated in independent studies, quantified in a range of foods and was found almost exclusively in citrus fruits (Scalbert et al., 2014). This case-study example and many others now demonstrate that metabolomics is an efficient approach to discover new reliable biomarkers of food intake in a data-driven approach. In total, more than 145 candidate biomarkers have been proposed for about 20 foods through these food metabolome studies, and interestingly about 75% were phytochemical metabolites (Scalbert et al., 2014). These candidate metabolites must be validated as it has been done for proline betaine.

Since interventional studies for all the foods of the human diet are not feasible, the use of cohort samples to identify candidate intake biomarkers for a range of foods at the same time can be performed. The Phenotyping using Metabolomics for Nutritional Epidemiology (PhenoMeNEp) project (Rothwell et al., 2014) used the SU·VI.MAX2 cohort which is a well-characterized cohort of French adults and identified the strongest discriminant of coffee intake as Atractyligenine glucuronide, a phase II metabolite of a diterpene, which contributes to the bitter taste of roasted coffee and which has never been reported in significant amounts in any other food sources (Rothwell et al., 2014). Two others strong discriminants were alkaloids, the diketopiperazine cyclo (isoleucyl-prolyl) and trigonelline. The three biomarkers were classified as excellent biomarkers when their performance was assessed using receiver-operating characteristic (ROC) curves test. Certainly, metabolomics-derived coffee biomarkers will be used in the coming years, in particular to study the impact of coffee on cognition.

Therefore, profiling of urine or plasma metabolomes in interventions or cohorts studies is efficient to discover new candidate biomarkers of food intake with a data-driven approach. A large initiative, the FoodBAll project (http://foodmetabolome.org/) has recently been funded by the European Joint Programming Initiative Healthy Diet for Healthy Life, to identify a large range of new nutritional biomarkers using metabolomics and to develop a harmonized scheme for their validation. Beyond biomarker discovery, food metabolome profiling covering a wide range of bioactives and biomarkers of intake in biofluids may become a new method for nutritional assessment, once the current technical difficulties for rapid and complete profile annotation will be overcome.

5.3. Micronutrients

As reported by numerous studies in animals and humans, essential antioxidant trace elements such as Zinc (Zn), Selenium (Se) and/or insulin sensitizers (Chromium (Cr), Zn) are deeply implicated in brain protection. Selenoproteins, *i.e.* Selenoprotein P and

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Glutathione peroxidase, protect brain cells against oxidative stress. A low Se status increases the risk of cognitive decline. The greater is the decrease in plasma Se, the higher is the probability of cognitive decline as indicated in the study of Akbaraly et al. (Akbaraly et al., 2007). A potential preventive relevance for an optimal Se status can be therefore speculated to maintain a healthy brain [63]. However, there is an absence of consistent clinical evidence regarding whether Se supplementation is beneficial for the treatment of AD (Loef et al., 2011).

Zn also acts positively on brain health by improving insulin sensitivity and reducing inflammation and oxidative stress. However, so far no benefits on ageing brain are reported after Zn supplementation in humans and even a potential neurotoxic effect of Zn accumulation has been observed in AD patients (Nuttall and Oteiza, 2014).

Cr deficiency has resulted in insulin resistance and increased oxidative stress (Roussel et al., 2007). Indeed, in insulin resistant states (T2DM and MetS), increased Cr intakes are associated with improved cognitive functions (Krikorian et al., 2010).

5.4. Polyphenols and polyphenol-rich diets

A number of studies have observed protective associations between dietary polyphenols and the prevention of age-related chronic diseases such as CVD, diabetes, cancers, osteoporosis and neurodegenerative diseases (Arts and Hollman, 2005; Scalbert et al., 2005; van Dam et al., 2013). The strongest evidence of health-protective properties is for CVDs (Cassidy et al., 2013; Hooper et al., 2008; McCullough et al., 2012). However, the well-known biases and measurement errors of dietary assessment tools make the precision and accuracy of dietary intake estimations difficult, and therefore, the associations observed between polyphenols and health are compromised. As a result, it is still challenging to develop personalized diet-related recommendations for dietary polyphenol intake, and further research on the identification and validation of new nutritional biomarkers is warranted (Zamora-Ros et al., 2012).

In the epidemiologic InCHIANTI study (Invecchiare in Chianti, ageing in the Chianti area), the group of Andres-Lacueva investigated the associations between total urinary polyphenols, as biomarkers of total dietary polyphenols (Zamora-Ros et al., 2011), and all-cause mortality over a 12-year period among older adult participants (Zamora-Ros et al., 2013). Recently, they also investigated the associations between total polyphenols and cognitive decline over a 3-year follow-up in older participants free of dementia at baseline (Rabassa et al., 2015). In these studies, they observed that participants who consumed a diet rich in polyphenols (>600 mg/d) reduced the risk of all-cause mortality and the risk of cognitive decline in global cognitive function (using the mini-mental state examination), and in attention (using the Trail Making Test A), by 30%, 47% and 48%, respectively. By contrast, they did not reduce the risk of decline on executive function measured with the Trail Making Test B, as compared to those who consumed diets low in polyphenols (<500 mg/d). However, no association was observed between total urinary resveratrol metabolites, a biomarker of red wine consumption, and all-cause mortality (Rabassa et al., 2015).

In addition, research on ageing effects has revealed several signalling pathways which have been experimentally demonstrated to be involved in the regulation of the ageing process (Salminen and Kaarniranta, 2012). The central effects of these polyphenols, at the transcriptomic level confirmed the involvement of specific molecular component of the AMPK-autophagy systems also in neuronal and glial cells (unpublished data). The modulation of AMPK and autophagy could potentially prevent not only neurodegeneration, but also, in more general terms, it could promote healthy cognitive ageing.

Cinnamon polyphenols also deserve a special attention since they have been reported to reverse *in vitro* Tau protein aggregation and break up Tau filaments (Peterson et al., 2009). Interestingly, cinnamon added to the diet also counteracts the increase of amyloid precursor protein (APP) and Tau protein induced by a high fat/high fructose diet in the rat brain (Anderson et al., 2013).

Polyphenols intake is associated with consumption of fruits such as grapes, apples, pears, cherries and various berries contain between 200 and 300 mg of polyphenols per 100 g of fresh weight (Llorach et al., 2012). Moreover, a cup of tea or a large cup of coffee contains around 100 mg of polyphenols. Red wine, chocolate, legumes and nuts also contribute to the polyphenol intake. Recent development in analytical techniques and in metabolomics should allow the measurement of large sets of polyphenol metabolites as biomarkers of usual dietary polyphenol intake (Llorach et al., 2012). This will be essential if we are able, finally, to make dietary recommendations regarding polyphenols for improving the autonomy and quality of life in older people.

5.5. Flavonoids

Amongst polyphenols, the flavonoid subclass has been extensively studied. Given the wealth of available data for these phytochemicals, we decided to present those as a separate paragraph. Flavonoids, found in a variety of fruits, vegetables and beverages, have been recognized as promising agents capable of influencing different aspects of synaptic plasticity resulting in improvements in memory and learning in both animals and humans (Del Rio et al., 2013; Spencer, 2008; Williams and Spencer, 2012).

Accumulating evidence suggests that certain dietary flavonoids might delay the onset and/or slow the progression of AD (Williams and Spencer, 2012), but the precise identity of the bioactive form(s) involved is unknown and critical information about bioavailability and metabolism has hindered progress in the field. Despite significant advances in our understanding of the biology of flavonoids over the past 15 years, they are still mistakenly regarded by many as acting simply as antioxidants. Yet, flavonoids are much more likely to combat neuronal dysfunction and toxicity by recruiting anti-apoptotic pro-survival signalling pathways, increasing antioxidant gene expression, and reducing Aβ pathology (Williams et al., 2004; Williamson et al., 2012). There is, however, a lack of consensus as to the precise identities of the flavonoids capable of exerting these effects, partly because flavonoids have notoriously poor bioavailability and are extensively metabolised *in vivo*, but also because most *in vitro* studies use concentrations that are at least 100 fold higher than those found following dietary administration. The group of Williams has started to address some of these limitations by adopting unbiased *in vitro* screening strategies using flavonoids at concentrations that are potentially achievable in humans to mimic more closely what occurs *in vivo* as a first step towards identifying possible dietary interventions for AD (Cox et al., 2015). Using an APP-GAL4 gene reporter assay in primary rodent neurones to screen modulators of APP processing they identified a number of flavonoids that potently inhibit βγ-secretase activity. Most notably, the flavanols (−)-epicatechin (EC) and epigallocatechin reduced βγ-secretase activity and Aβ production at nanomolar concentrations and reductions in Aβ pathology were also observed following oral administration of EC to APP-PS1 mutant mice.

Since EC is readily absorbed and circulates primarily as glucuronidated, sulfated, and O-methylated forms in human plasma, the observed bioactivity is most likely to reside in an EC metabolite. Therefore, Williams' hypothesis was that dietary EC, acting as a *prodrug*, or alternatively a synthetic EC analogue based on a metabolite, had the potential to be developed into a prophylactic

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dietary supplement for AD. The molecular mechanism underlying this reduction in Aβ production both in wild-type neurons and in a transgenic model of AD is not clear but Williams et al. presented evidence suggesting that EC inhibits the β-site amyloid precursor protein cleaving enzyme 1 (BACE1) (Cox et al., 2015).

A large body of evidence has also emerged from human intervention studies demonstrating that the consumption of flavonoid-rich foods is associated with cognitive benefits (for a review see (Macready et al., 2010; Williams and Spencer, 2012)). The mechanisms by which flavonoids exert these actions on cognitive performance are being elaborated, with evidence suggesting that they may modulate the activation status of neuronal receptors, signalling proteins and gene expression (Rendeiro et al., 2012, 2013; Williams et al., 2008). Although whether these effects are mediated directly (*i.e.* within the brain) or from the periphery is currently unknown.

There is considerable evidence suggesting that neuronal activity during cognitive performance is tightly coupled to increases in regional blood flow, a process known as cerebrovascular coupling (Attwell et al., 2010). Such processes are primarily mediated by nitric oxide (NO) generated by the activation of both endothelial nitric oxide synthase (eNOS in endothelium) and neuronal nitric oxide synthase (nNOS in neurons) (Toda et al., 2009). In particular, NO derived from eNOS activation contributes to cerebral arterial dilatation, by migrating to vascular smooth cells and increasing blood flow at the blood-brain interface (Atochin and Huang, 2011). Furthermore, there is increasing evidence suggesting that the cerebrovascular response is also mediated by NO liberated from nNOS-containing neurons adjacent to intra-cerebral arterioles and capillaries (Schroeter et al., 2006).

There is substantial evidence which supports the beneficial effects of flavonoids, in particular flavanols (Schroeter et al., 2006, 2010) and anthocyanins (Rodriguez-Mateos et al., 2013) on peripheral vascular function and blood flow (measured using flow mediated dilatation). These effects are mediated by the actions of absorbed flavonoid metabolites on NO bioavailability, *via* their potential to activate eNOS (Schroeter et al., 2006) and/or inhibit NADPH oxidase activity (Rodriguez-Mateos et al., 2013). Such improvements in vascular function occur acutely *e.g.* flavanols (cocoa, tea; 1–3 h) (Schroeter et al., 2006) and anthocyanins (blueberry; 1–2 h and 5h+) (Rodriguez-Mateos et al., 2013), are in the same timeframe and show cognitive improvements using similar interventions type. Furthermore, flavonoid-induced improvements in spatial memory in animal models (Rendeiro et al., 2012; Williams et al., 2008) share similarities with those of exercise-induced alterations in synaptic plasticity in the brain (Bechara and Kelly, 2013; Cotman et al., 2007), as both involve the activation of Akt/PKB and the increased expression of BDNF (Spencer, 2009). Indeed, Akt/PKB activates both eNOS and nNOS, *via* increases in intracellular Ca^{2+} levels in endothelial and neuronal cells, respectively (Dimmeler et al., 1999; Rameau et al., 2007) and thus, that may represent a common path by which flavonoids and exercise facilitate cognitive improvements. The central role that NO plays in flavonoid-induced improvements in human cognition and cerebral blood flow has been explored by the use of NOS inhibitors, which block the conversion of L-arginine to L-citrulline and inhibit NO production (Iadecola et al., 1994). Future studies should utilize L-arginine analogues such as nitro-L-arginine methyl ester, nitro-L-arginine, and L-N^{G}-mono-methyl-arginine (L-NMMA) to help provide information on the role of NO and blood flow in mediating cognitive activity of polyphenols. Use of L-NMMA in humans has been shown to result in a fall in cerebral blood flow (Shabeeh et al., 2013) without altering basal metabolic activity (Kelly et al., 1994). The use of NOS inhibitors *in vivo* has the potential to assess the contribution that NO plays in mediating increases in cerebral blood flow and hyperemic responses to cognitive activity in response to flavonoid intervention. Applying such an approach to polyphenol clinical trials will provide a clearer mechanistic understanding of how flavonoid intake acutely mediates cognition and how such transient blood flow alterations may underpin longer-term improvements in humans.

Recent datasets indicate that high flavanol intake (495 mg) is associated with improvements in human executive function and episodic memory at 2 h post-consumption, compared to a low flavanol control (23 mg) (Lamport et al., 2015). Similar data following anthocyanin intake (755 mg; delivered and controlled as blueberry) indicate that cognitive improvements are manifested at 5 h post intake reaching significance already at 1 h (Lamport et al., 2015). The time-course of these cognitive effects, along with Spencer's recent peripheral vascular function/blood flow data, using flow-mediated dilatation (FMD) (Rodriguez-Mateos et al., 2013) suggested that the modulation of peripheral blood flow and cerebrovascular blood perfusion by flavanol-rich foods may mediate acute improvements in cognition. In support of this hypothesis, recent pilot data indicate that flavanol intake (495 mg) is capable of increasing cerebral blood perfusion within select regions of the brain, as measured by arterial spin labelling (Lamport et al., 2015) in a timeframe consistent with both peripheral vascular and cognitive test performance. Further, a memory testing procedure known as pattern separation has recently been identified which has the potential to demonstrate therapeutic response in men to compounds which promote hippocampal neurogenesis (Bakker et al., 2008; Yassa et al., 2011). A paper has just appeared demonstrating that one of such tests was able to identify positive effects of a high-flavanol cocoa preparation in elderly healthy volunteers (Brickman et al., 2014). In this study, improved cognitive function with the cocoa preparation was accompanied by functional magnetic resonance imageing (fMRI) evidence of enhanced activity in the *dentate gyrus* which is the hippocampal site responsible for neurogenesis. However, to date, no cause-effect relationship has been investigated between flavonoid intake, vascular function and cognitive performance. In addition, very little is known about the longer-term effects of flavonoids on cognitive function in humans, or whether such effects may be sustained in the absence of intake, despite there has been a wealth of animal data in support of potential longer term efficacy (Corona et al., 2013; Rendeiro et al., 2012, 2013; Williams et al., 2008).

Despite clear evidence regarding the acute vascular effects of flavonoids shown in humans (Macready et al., 2010) and medium-term changes in synaptic plasticity markers demonstrated in animal studies (Spencer, 2009), the basic mechanisms of action of flavonoids in humans remains unclear, due to a lack of precise causative/mechanistic data. Future work should strive to determine the mechanistic basis of flavonoids-induced improvements in cognitive function by investigating the degree to which peripheral- and cerebral blood flow induced by flavonoids metabolites plays in determining improvements in human cognitive performance, in particular attention and episodic memory.

5.6. Vitamins

Among vitamins, high dietary intakes of tocopherols are associated with a reduced AD or dementia incidence (Mangialasche et al., 2011). However, interventional studies using Vitamin E supplementation failed to report positive effects on the risk of AD (Barnard et al., 2014) for vitamin C, although there has been inconsistency among observational studies relating dietary intake of ascorbic acid to improved cognition, some results have favoured an important role for ascorbic acid in cognitive health. Therefore, further research focused on investigating the specific role of ascorbic acid in AD with special attention to the study design and methodologies, which rep-

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resent an important study limitation, has been suggested to provide more conclusive data (Harrison et al., 2014).

The mechanisms that support the relation between vitamins B and the brain are mostly related to homocysteine (Hcy) metabolism, a marker of vitamin B insufficiency. Hcy is catabolized through a remethylation cycle mediated by folate and vitamin B12, which provides methyl-group for several metabolic steps (Levitt and Karlinsky, 1992). Clinical evidence has demonstrated a correlation between elevated plasma (Hcy) and the occurrence of AD and thus, hyperhomocysteinemia has been suggested as an important risk factor of AD (Obeid and Herrmann, 2006; Seshadri et al., 2002). Observational studies have reported that people with high blood concentrations of Hcy have elevated risk for vascular disease (Clarke et al., 1991) and AD (Clarke et al., 1998). These studies prompted randomized trials to assess whether vitamins B positively impacted on cognition, but their results have been mixed. In one of the most recent systematic reviews, 35 cohort studies with a total number of 14,235 individuals were identified (O'Leary et al., 2012). Twenty-one studies were of good quality of which only 7 showed a beneficial association. This association was more consistent in studies that included the newer and more specific markers of vitamin B12 status such as methylmalonic acid (MMA) and holotranscobalamin (holoTC). The most recent Alzheimer's Disease International (ADI) report on nutrition and dementia included 4 additional studies that all showed a beneficial association of a higher vitamin B status with less cognitive decline (Alzheimer's Disease International, 2014). Even after including those more recent studies still the majority of observational studies did not show a beneficial association. A *meta*-analysis was performed on RCTs performed in individuals with or without cognitive impairment (Ford and Almeida, 2012). Nineteen RCTs were included and the overall conclusion was that no effect of vitamin B supplementation was observed on cognition. Similar findings were reported in an earlier Cochrane review (Malouf and Areosa Sastre, 2003), which concluded that 4 RCTs provided no evidence for improvement in people with cognitive impairment or dementia when treated with folic acid with or without vitamin B12 or B6. However, a later Cochrane update (Malouf and Grimley Evans, 2008), which included 8 studies concluded that there was some effect. For instance, a better response to cholinesterase treatment with B vitamins was observed in some studies including both people with AD and without dementia.

After these reviews some additional RCT results were published (Douaud et al., 2013; Hankey et al., 2013; Walker et al., 2012) of which two RCTs showed an effect. Several observational studies have included brain MRI and all showed at least some beneficial associations (de Lau et al., 2009; Sachdev et al., 2002; Smith et al., 2010; Tangney et al., 2011; Vogiatzoglou et al., 2008).

Some other conflicting results have been released by the Folate after Coronary Intervention Trial (FACIT) (n = 800) which reported that folic acid had a significant effect on memory (Durga et al., 2007). This study showed that people who were treated with folic acid and had high levels of Hcy (which is a risk factor for dementia and heart disease) had better cognitive function over a 2–3 years period than those who were not treated.

One recent RCT (VITACOG trial) including 168 MCI patients has been performed that included brain MRI as an outcome measure and showed that after 24 months of vitamin B supplementation patients showed a 30% slower rate of brain atrophy (Smith et al., 2010). Additionally, in the same study it was demonstrated that vitamin B supplementation was able to slow the cognitive and clinical decline in people with MCI, in particular in those with elevated Hcy levels (de Jager et al., 2012). Despite this, reliable evidence requires large trials, avoidance of bias and sub-group analysis and *meta*-analyses of such trials. A recent *meta*-analysis by Clarke et al. (Clarke et al., 2014) included all B-vitamin trials assessing effects on cognitive function. It assessed the effects of B-vitamins on individual domains of cognitive function, global cognitive function and cognitive ageing. Dietary supplementation with vitamins B to lower Hcy levels had no significant effect on individual domains, global cognitive function or cognitive ageing. Overall, it was shown that vitamins B had no beneficial effect on either cognitive ageing (Clarke et al., 2014) or vascular disease (Clarke et al., 2010).

Another vitamin that has been widely investigated is vitamin D. Currently a large proportion of populations are vitamin D deficient, and in particular the elderly (van der Wielen et al., 1995). Some vitamin D receptors are located in the brain and many mechanisms that may support its role in the brain have been identified (Brouwer-Brolsma and de Groot, 2015). Regarding observational evidence, Balion et al. (2012) identified 37 studies that could be included in his *meta*-analysis. There was a large heterogeneity, in particular in different cognitive tests that were used as an outcome measure. Results based on 8 studies using the MMSE showed that participants with 25-hydroxyvitamin D (25(OH)D) concentrations >50 nmol/L had a higher MMSE score than those with concentrations <50 nmol/L.

5.7. ω-3 PUFAs

Long-chain ω-3 PUFAs, EPA and DHA have been associated with decreased brain inflammation and preservation of the integrity and function of neuronal membranes (Janssen and Kiliaan, 2014).For example, DHA which is a key component of phospholipid cell membranes, may modulate the amyloid precursor protein (APP), thereby reducing formation and increasing clearance of β-amyloid, the main component of AD plaques (Alzheimer's Disease International, 2014).

Observational evidence has been focused on the association between fish long-chain ω-3 PUFA intake or ω-3 PUFA status and cognitive functioning, cognitive decline or dementia. More than 30 studies have been performed and the vast majority of studies have showed beneficial associations (van de Rest et al., 2012). In the first Cochrane review on ω-3 PUFA trials that was published in 2006, no single RCT could be included (Lim et al., 2006). That review was updated in 2012 and at that time the first RCTs in non-demented elderly and with a study duration of at least 6 months were published. In total, three RCTs were included with a total of 3536 participants. The conclusion was that ω-3 PUFA supplementation had no effect on cognitive functioning (Sydenham et al., 2012). In the same year Mazereeuw et al. (2012) performed a *meta*-analysis and included cognitively impaired and demented individuals as well. They included 10 RCTs and did not see an overall benefit for immediate recall after ω-3 PUFA supplementation in healthy or demented elderly. However, they found an effect on the specific cognitive domains for immediate recall, attention and processing speed in cognitively impaired non-demented individuals.

The research field is currently advancing by not only the inclusion of batteries of cognitive tests as an outcome measure, but also including MRI techniques. Several observational studies including brain MRI have been performed and all have showed at least some beneficial associations (Conklin et al., 2007; Pottala et al., 2014; Samieri et al., 2012; Tan et al., 2012; Titova et al., 2013; Virtanen et al., 2008). Also, one RCT has been performed in 65 healthy elderly and with a study duration of 26 weeks (Witte et al., 2013). In this study beneficial effects were found on executive functioning, on the MRI measures of gray matter atrophy, and on white matter microstructural integrity.

5.8. Calorie restriction

Diet including total intake, frequency, and content has emerged as an important environmental factor that can impact brain plas-

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ticity, including adult hippocampal neurogenesis (AHN) (Stangl and Thuret, 2009; Zainuddin and Thuret, 2012). The level of AHN decreases with age and has been linked directly to cognition and mood (Murphy et al., 2014). In rodents, an increase of neurogenesis in the hippocampus is associated with improved learning/memory abilities, whereas a decrease is associated with symptoms of depression (Mateus-Pinheiro et al., 2013; Snyder et al., 2011). Therefore, modulation of AHN by diet emerges as a potential mechanism by which nutrition impacts on mental health (Murphy et al., 2014). Synapse formation is a key site in the initiation of the neurodegenerative process occurring during AD pathology, and then, calorie restriction (CR) may have significant effects on the disease pathology *via* modulation of AHN and synaptic plasticity (Maruszak et al., 2014). Wu et al. (2008b) found that CR (30% for 4 months) in the transgenic mouse model of AD significantly attenuated ventricle enlargement, hippocampal atrophy, and caspase-3-activation. For example, the effect of CR, limiting the intake compared to baseline unrestricted or *ad libitum* consumption, together with maintained levels of vitamin, mineral, or other essential biomolecules has appeared to increase AHN. Furthermore, CR seems to improve the resilience of synapses to metabolic and oxidative damage and modulates the structure and functional status of synapses (Mattson, 2012). Moreover, CR has demonstrated to induce the differential expression of genes of which 25% are involved in synaptic plasticity (Park and Prolla, 2005). Mice have showed improved working memory after long-term CR (Kuhla et al., 2013; Steinman et al., 2011). An increase in the expression of NMDA receptors, essential for LTP and synaptic plasticity, has been found in the hippocampus of 60% CR obese rats as compared to age-matched *ad libitum* fed animals (Yilmaz et al., 2011). Taken together, while still further research is warranted to elucidate the mechanisms by which some dietary factors induce brain plasticity, animal and supported epidemiological studies have demonstrated that multiple dietary regimens and components increase the levels of AHN, enhance brain plasticity and promote synaptic function in the context of ageing.

5.9. Ketogenic diets

Very-low-carbohydrate ketogenic diets (VLCKD) have been used for many decades especially after the 1970s when they became popular for weight loss (Atkins, 1972). But it was in the early 1920s when the importance of the use of these diets became relevant from the clinical point of view and were successfully used to treat many pathological conditions such as epilepsy (Hartman et al., 2007), diabetes (Dashti et al., 2006), CVD factors (Paoli et al., 2011) and neurological diseases (Baranano and Hartman, 2008). The review by Paoli et al. (2013) considers possible mechanisms for the therapeutic actions of the ketogenic diet (KD) on weight reduction and different diseases such as CVD and diabetes. Although, the exact mechanisms of action of the KD are still poorly understood recently reports have suggested that ketone bodies (KB) act as neuroprotective agents by raising ATP levels, diminishing the production of reactive oxygen species in neurological tissues and enhancing the regulation of synaptic function though mitochondrial biogenesis (Bough and Rho, 2007). Moreover, the stimulation of PUFAs synthesis by a KD has been demonstrated to regulate neuronal membrane excitability mediated by voltage-gated sodium channels (Huffman and Kossoff, 2006).

However, new research concerning one of these diets, the MCT ketogenic diet, has recently demonstrated a compelling mechanism of action in seizure control (Chang et al., 2015). These studies show that a fatty acid provided in the diet, decanoic acid (10:0), reduces seizures induced in hippocampal slices of rodent. Using the whole cell patch clamp with rat hippocampal slices, decanoic acid reduced excitatory postsynaptic currents by $38.9 \pm 5.5\%$ at 52 μg/mL concentration and inhibited α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors, which are a target for antiepileptic drugs. This inhibitory mechanism is specific to defined chemical structures, is effective against multiple AMPA subunit compositions, and is enhanced during synaptic activation. These results define how the MCT diet provides a way of controlling seizures by the diet, without the need for the production of ketones or for pharmacological intervention (Chang et al., 2015, 2013).

Given that patients with AD show a higher incidence of seizures (Palop and Mucke, 2009), KD may be a successful diet for its clinical treatment. Supporting evidence suggests that acute elevation of serum β-hydroxibutyrate (β-OHB) (one type of KB) through an oral dose of MCTs shows cognitive improvements in AD patients. A recent RCT in 20 patients (55–58 years) diagnosed with probable AD (n = 15) or MCI (n = 5) showed that acute administration of MCTs (40 g), which led to elevate β-OHB, was positively correlated to improved cognitive function (Reger et al., 2004). Another clinical trial performed in 152 patients with mild to moderate AD (Henderson et al., 2009) compared the effect of Axona®, a medical food containing a formulation of MCTs, or placebo and found that cognitive scores remained stabilized in the Axona® group, while the placebo groups presented a decline in cognition, but only among Apoε4(−) subjects. Although, Axona® formulation has been reported to be well-tolerated in normal elderly volunteers, the proposed cognitive effect is uncertain in non-demented elderly people. Importantly, all these cognitive responses to increased energetic substrates were strongly dependent on APOE genotype (Craft et al., 2000).

5.10. Multicomponent diets

The important role of diets and healthy lifestyle in the prevention of vascular disease development is widely accepted. Already 30 years ago pioneering studies on Greenland Eskimos indicated that intake of ω-3 long chain polyunsaturated fatty acids (ω-3 LCPUFAs) from fish and wildfowl had protective effects against CVD (Bang et al., 1971, 1980). More recently, the Mediterranean diet containing fish, olive oil and nuts as important lipid containing components, has been shown in several prospective worldwide studies to be inversely associated with CVD (Estruch et al., 2013) and to have a strong protective function against hypertension, obesity, and AD risks (Calton et al., 2014; Grosso et al., 2014; Koliaki and Katsilambros, 2013; Scarmeas et al., 2009). Moreover a recent thorough systematic review and *meta*-analysis suggests that a higher adherence to the Mediterranean diet may affect not only the risk of AD, but is also associated with a reduced risk of developing MCI and AD, and a reduced risk of progressing from MCI to AD (Singh., et al., 2014; Solfrizzi and Panza, 2014).Dietary lipids are also starting to be highly recognized in nutrition thanks to their direct actions on synaptic function and cognitive processes (de Waal et al., 2014; Kamphuis and Scheltens, 2010; Shah, 2011; Shah et al., 2013; van Wijk et al., 2014; Wurtman, 2008). Contrarily, diets high in saturated fat are becoming notorious for reducing molecular substrates that support cognitive processing and increasing the risk of neurological dysfunction in both animals and humans (Gomez-Pinilla, 2008; Li et al., 2013; Wu et al., 2008a). Dietary factors can affect multiple brain processes by regulating neurotransmitter pathways, synaptic transmission, membrane fluidity and signal-transduction pathways. Recent data published by the group of Kiliaan et al. (Jansen et al., 2014; Wiesmann et al., 2013; Zerbi et al., 2014) and latest data in mice models for AD and vascular impairment, have shown that the treatment with multicomponent diets promotes neuroprotection by decreasing inflammation, restoring cerebral blood flow and volume, inhibiting neurodegeneration, and enhancing neural plasticity by increasing neurogenesis (Wiesmann et al.,

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2016). In particular, they (Zerbi et al., 2014) showed that a specific combination diet (Fortasyn™) containing membrane precursors such as ω-3 fatty acids and uridine monophosphate plus cofactors for membrane synthesis was able to inhibit/reverse the early functional connectivity reduction and cerebral blood flow (CBF) impairment in mice (both parameters were apparent already before cognitive decline).

Thus, diet may serve as preventive strategy at very early, non-symptomatic phases of AD, especially because there are no currently effective treatments for AD. Therefore, future research should focus on the early, asymptomatic phase of the disease especially on the (cardio) vascular risk factors like atherosclerosis, hypertension, obesity and T2DM being modifiable *via* changes in lifestyle factors such as diet.

5.11. Exercise

Gradual and progressive memory decline is often one of the earliest hallmarks in AD which can strongly influence the quality of life of an individual. Several lifestyle factors may interfere with the rate of cognitive decline in the elderly such as diet and physical activity.

The Study of Elderly's Memory impairment and Associated Risk factors (SEMAR) has been set up in Indonesia and included 719 participants (aged 52–99 years) from different ethnic backgrounds in rural and urban Java (Jakarta, Citengah and Yogyakarta) (unpublished data). These cohorts as well as other similar cohorts in China, Netherlands, UK and USA, have recently been set up to investigate whether lifestyle factors in different ethnic/cultural cohorts were associated with a reduced risk of dementia (ongoing study) and found that the combination of exercise and eating fruit had a cumulative effect in reducing dementia risk in Indonesia people (unpublished data).

Many observational studies (Clifford and Hagervorst, 2009; Hogervorst et al., 2012) have showed a reduced risk of dementia in people who exercise. For instance, in Indonesia it was found that older people who engaged in sports had a halved risk of dementia (Hogervorst et al., 2012), which was similar to data from the US and other countries (Barnes and Yaffe, 2011). However, several reviews have also showed that only 50% of the studies including an exercise intervention showed cognitive improvement in older people (Clifford and Hagervorst, 2009; Hogervorst et al., 2012) which might be due to poor adherence to the program. Similarly, the group of Hogervorst et al. (2012) found that resistance band (muscle strength) exercises 2–3 times/week for 20–30 min improved memory function. In addition, exercise may be effective as a preventive activity as it can lower blood pressure and total cholesterol, can reduce abdominal fat and improve immune and lung function, as well as improve cardiovascular function, which improves cerebral blood flow. As discussed previously, all these factors may be implicated in dementia. Importantly, exercise can also directly promote outgrowth of nerve cells which allows better communication between brain cells, which is often reduced in dementia (Clifford and Hagervorst, 2009). Even in people who have already developed dementia, walking and muscle strengthening exercises are likely to have positive effects on cognitive abilities (Hogervorst et al., 2012).

In conclusion, risk factors for AD are similar to those for CVD (heart), such as high blood pressure, smoking, high cholesterol and obesity and need to be treated in midlife at the latest to reduce the risk of dementia later in life. A multi-disciplinary change in lifestyles (combining exercise with healthy diets) with a focus on midlife is the most important factor for prevention of dementia. Therefore, changing the lifestyle to a healthier one which includes exercise and a healthy diet can reduce the risk for both heart disease and dementia.

6. Methodological challenges in nutritional interventions on cognition

Epidemiological studies have shown that a lower risk of dementia or cognitive decline is associated with diets relatively low in energy (Luchsinger et al., 2002) but rich in several key nutrients and food derived non-nutrient bioactives, including long-chain ω-3 PUFA (Cunnane et al., 2009; Dacks et al., 2013), vitamins B (Clarke, 2008), antioxidants such as vitamins C, E (Mangialasche et al., 2010) and carotenoids (Li et al., 2012), and polyphenols (Joseph et al., 2009). However, most RCTs that have administered these dietary components as supplements have yielded disappointing results on cognition so far, (Barberger Gateau et al., 2013; Clarke et al., 2014; Sydenham et al., 2012). There are, however, some notable interest, particularly in the Memory Improvement with DHA Study (MIDAS) (Yurko-Mauro et al., 2010), the Souvenaid® combination of nutrients in mild AD (Olde Rikkert et al., 2015; Scheltens et al., 2010, 2012), and the Prevention with Mediterranean Diet (PREDIMED) study (Valls-Pedret et al., 2015). Thus, epidemiological data and these "success stories" from a limited number of RCTs, provide the justification and valuable methodological insight. In addition, they could be used in combination with the implementation of more robust 'fit-for-purpose' RCTs to demonstrate the impact of diet on cognition in older persons. Such interventions should be carefully powered and of adequate duration (chosen based on physiological insights into likely changes in the primary outcome measures during the intervention period) in order to prevent false negative findings. Three further aspects should be considered: 1) improving inclusion criteria in RCTs, 2) optimizing the composition of the nutritional supplement or the diet to be evaluated, and 3) defining more sensitive primary and secondary outcomes which are also important methodological considerations that will be discussed below.

Identification of individuals at high risk of cognitive decline or dementia, who should be included in RCTs assessing the impact of nutrition, who are likely to be sensitive and gain most benefit from the intervention should be based on early markers of disease progression, low dietary intake or blood levels of selected dietary components of interest, or genetic characteristics. The natural history of the pathophysiology of AD spreads over decades during which Aβ accumulates in the brain before the first cognitive symptoms appear (Jack et al., 2013, 2010a,b) raising the question of the optimal window for prevention or the progression from the preclinical, 'at-risk' phase to a clinical diagnosis of disease. It is virtually impossible to demonstrate the efficacy of primary prevention in regard to cognitive decline. Thus, the main target of RCTs should be the secondary prevention, at a very early stage of cognitive decline. The MIDAS included middle-aged adults (aged 55 years) with a subjective memory complaint and preserved general cognitive function but a logical memory baseline score lower than that of normal younger adults (Yurko-Mauro et al., 2010) to explore the effect of DHA consumption (900 mg/day) for 24 weeks. These individuals also had low regular fish consumption, less than 200 mg/day DHA. After completion of the trial, those receiving DHA, scored significantly higher on several tests of memory than the control group. The use of genetic variation as an inclusion/exclusion criteria could also be considered, since several epidemiological studies and at least one RCT have suggested that the benefit of supplementation with DHA on cognition could be limited to non-carriers of the ε4 allele of the *APOE4* gene, the main genetic risk factor for AD (Barberger Gateau et al., 2011).

Epidemiology also allows characterization of healthy diets providing optimal combinations of foods and nutrients that are associated with better cognitive performance (Alles et al., 2012), providing the rationale for RCTs using combinations of supplements rather than single nutrients. The most famous example is the

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Mediterranean diet, which has been associated with lower risks of dementia or cognitive decline in several epidemiological studies, mostly in Europe and the US (Feart et al., 2010; Lourida et al., 2013; van de Rest et al., 2015). However, there is great heterogeneity in the definition of the "Mediterranean diet" between studies especially in non-Mediterranean countries. The PREDIMED NAVARRA RCT in Spain, demonstrated that randomized participants who followed a Mediterranean diet enriched with virgin olive oil or nuts scored significantly better than the control group following a low-fat diet on a global cognitive score 6.5 years later (Valls-Pedret et al., 2015). Few RCTs have evaluated the impact of multivitamin supplements on cognition (Grima et al., 2012). For instance, Souvenaid® which contains ω-3 PUFA (EPA and DHA), B-vitamins, a mixture of antioxidants, and uridine monophosphate (UMP), was formulated to improve synapse formation and function (Cansev et al., 2015; Wurtman et al., 2009). A 24-week RCT conducted in patients with mild AD showed that the group receiving Souvenaid® scored significantly better than the placebo group on the memory domain of the neuropsychological test battery, the primary outcome (Scheltens et al., 2012). The study also showed improvement on measures of functional connectivity (Scheltens et al., 2012), functional brain network organization (de Waal et al., 2014), and sustained memory improvement until 48 weeks in an open label extension study (Olde Rikkert et al., 2015). This was the second study in mild AD with this intervention and confirmed the results of a proof-of-concept study which showed improved memory performance after 12 weeks (Scheltens et al., 2010). As these studies were conducted in subjects with early AD, more research is needed to define the optimal combination and doses of nutrients that could contribute to delay cognitive decline in older persons without AD diagnosis.

In the case of EPA + DHA, vitamin D and B vitamins, although there is relatively consistent epidemiological evidence to exhibit their independent impacts on cognition, RCTs have generally failed to demonstrate any efficacy.

Identification of relevant and sensitive biomarkers of disease progression, based on knowledge of the specific molecular and physiological targets of the intervention of interest, can optimize the choice of primary and secondary outcomes in RCTs. MRI and fMRI can provide evidence of the impact of nutrients on brain structure and function The rate of brain atrophy was the primary outcome of the Hcy and B vitamins in cognitive impairment (VITACOG) study (Smith et al., 2010) which found that vitamin B intake in the active treatment group was associated with 30% less brain atrophy per year than in those receiving the placebo. The effect on brain atrophy and cognitive function was mainly observed in those with higher baseline homocysteine levels, which were lowered by vitamin B treatment (de Jager et al., 2012; Smith et al., 2010). However, some RCTs have yielded discordant results regarding their impact on mechanisms of action and cognition. The concentration of F2-isoprostane in CSF, a marker of oxidative stress (lipid peroxidation), has been proposed as a sensitive but not specific biomarker of age-related brain injury (Li et al., 2014). In an RCT, 78 patients with mild to moderate AD were randomized to receive a high dose antioxidant mixture (800 IU/d vitamin E, 500 mg/d vitamin C, and 900 mg/day α-lipoic acid) or 400 mg/d Coenzyme Q, another antioxidant compound, or a placebo (Galasko et al., 2012). After 16 weeks, those receiving the antioxidant mixture had significantly decreased F2-isoprostanes in CSF as expected, but an accelerated cognitive decline. Thus, biomarkers should always be used in combination with cognitive outcomes.

This lack of positive results in RCTs may be due to too short trial duration, not appropriate target group, use of an inadequate dose, lack of efficacy of single nutrients and/or not sufficiently sensitive methodology to measure the outcomes. However, the identification of all these limitations will allow a better performance of future intervention trials. In addition, there is still need for well-designed trials that: a) have long intervention periods (at least >1.5 year), b) target at risk groups (mild cognitively impaired or nutrient deficient subjects), c) use harmonized cognitive test batteries (de Jager et al., 2014), d) include biomarkers and/or imaging measures, e) use a multi-nutrient or food pattern approach or a multi-domain approach, and f) whose design is aligned with specific mechanisms. Findings from epidemiological studies can be used to design more efficient RCTs assessing the impact of combinations of nutrients in well-targeted individuals, using both biomarkers and cognitive assessment as outcomes (Table 1).

Table 1
Contribution of epidemiology to design more efficient RCTs assessing the impact of nutrition on cognition.

What epidemiology tells us	What RCTs should do
Lower intake or blood levels of some nutrients are associated with higher risk of cognitive decline or dementia	⇒Target individuals with specific nutritional insufficiency, based on dietary or biological data
Significant cognitive decline is a late event in neurodegenerative diseases	⇒Target at risk individuals with more sensitive neuropsychological tests and biomarkers
Interaction between ω-3 PUFA status and APOE4	⇒Stratify RCTs according to APOE4 genotype and probably other single nucleotides polymorphisms (SNPs)
Healthy diets are associated with lower risk of cognitive decline or AD	⇒Use dietary supplements providing similar combinations of nutrients
AD is a multi-factorial disease whose natural history spreads over decades	⇒Use early and specific outcomes: – biomarkers of disease progression – biomarkers of mechanisms of action (oxidative stress, inflammation, insulin resistance, lipids. . . *etc.*) in combination with cognitive outcomes

7. Conclusion

Decline in cognitive abilities with age occurs in healthy individuals throughout the adult lifespan. Moreover, the line between normal and pathological ageing is not well-defined as neurological diseases start years before any clinical symptoms arise. Several health conditions such as CVD, diabetes or obesity are closely related to cognition. Therefore, when identifying dietary approaches to promote healthy brain ageing a holistic approach should be considered including nutrition, exercise and lifestyle factors, which not only target the brain but also overall cardiometabolic health (Fig. 1).

The mechanisms associated with normal ageing, including oxidative stress, neuroinflammation and vascular dysfunction are the same as those contributing to the development of neurological diseases. However, in these pathological conditions, the mechanisms contributing to ageing are exacerbated and triggered by different factors which might be genetic or environmental.

Preclinical studies in animals have consistently demonstrated the positive impact of several dietary components on cognitive performance and epidemiological studies have showed successful association of select dietary patterns with cognitive status. Particularly there is reasonable evidence that consuming Mediterranean-style diets protects against cognitive impairment. RCTs approaches have showed mixed results with intervention with single dietary components generally disappointing while some multi-nutrient/non-nutrient interventions have yielded more encouraging results. These observations are consistent with the results from epidemiological studies indicating that an adherence to dietary patterns, rather than adequate intake of single

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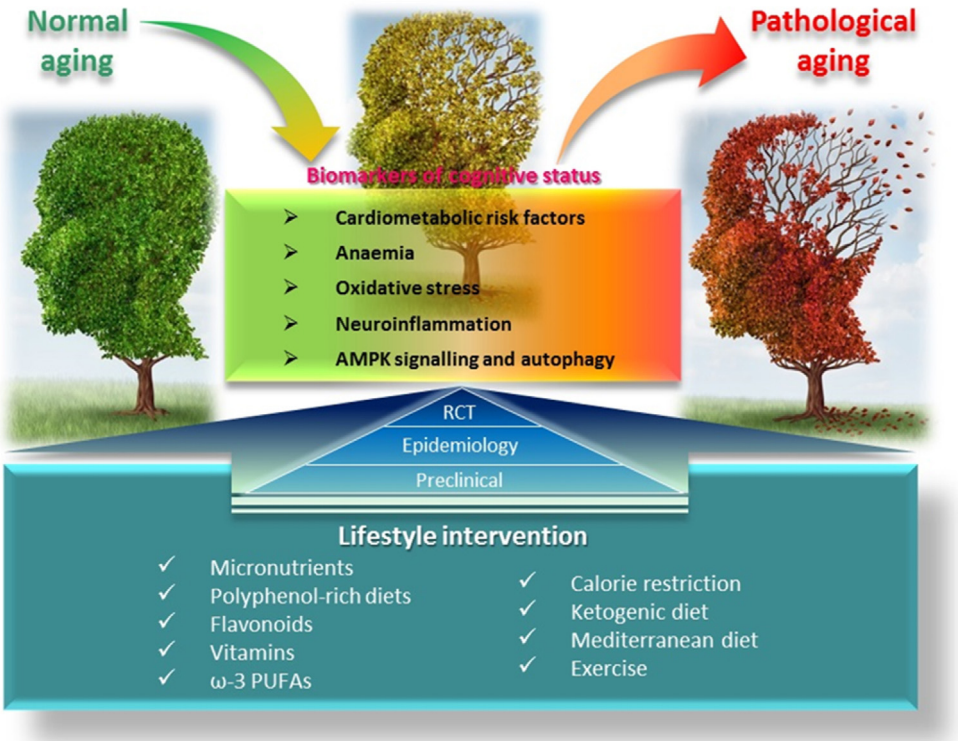

Fig. 1. Overview of links between lifestyle interventions on cognition and healthy brain function during ageing.

dietary components may be the most effective means of protecting against cognitive decline. A major objective of future research is to define the nutritional requirement for healthy cognitive ageing, and to translate these into effective dietary recommendations.

RCTs are the gold standard to probe the efficacy of drugs but it may not be the same for dietary components. In terms of primary prevention, it is logistically difficult to establish the effect of nutrition on cognition through RCTs which would require participants follow up for potentially decades. In terms of secondary prevention, targeting individuals at high risk of cognitive decline and learning from epidemiology as suggested in the last section of this review should allow a relatively rapid impact on cognition to be established.

Finally, it is the aim of this group to continue with the revision of the state of the art on nutrition for the ageing brain by organizing a follow-up workshop. In particular, mechanisms of ageing and their interaction with nutrients will be revisited, and new avenues and mechanisms of cognitive ageing that may be influenced by nutrition will be identified.

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