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Review

Nutrition and the ageing brain: Moving towards clinical applications

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ABSTRACT

The global increases in life expectancy and population have resulted in a growing ageing population and with it a growing number of people living with age-related neurodegenerative conditions and dementia, shifting focus towards methods of prevention, with lifestyle approaches such as nutrition representing a promising avenue for further development.

This overview summarises the main themes discussed during the 3rd Symposium on "Nutrition for the Ageing Brain: Moving Towards Clinical Applications" held in Madrid in August 2018, enlarged with the current state of

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knowledge on how nutrition influences healthy ageing and gives recommendations regarding how the critical field of nutrition and neurodegeneration research should move forward into the future.

Specific nutrients are discussed as well as the impact of multi-nutrient and whole diet approaches, showing particular promise to combatting the growing burden of age-related cognitive decline. The emergence of new avenues for exploring the role of diet in healthy ageing, such as the impact of the gut microbiome and development of new techniques (imaging measures of brain metabolism, metabolomics, biomarkers) are enabling researchers to approach finding answers to these questions. But the translation of these findings into clinical and public health contexts remains an obstacle due to significant shortcomings in nutrition research or pressure on the scientific community to communicate recommendations to the general public in a convincing and accessible way. Some promising programs exist but further investigation to improve our understanding of the mechanisms by which nutrition can improve brain health across the human lifespan is still required.

1. Introduction

The global increases in life expectancy and population have resulted in a growing ageing population and with it a growing number of people living with age-related neurodegenerative conditions and dementia. Age-related neurodegenerative conditions have an enormous societal and emotional cost. The prevalence of dementia worldwide is suspected to be as many as 50 million cases[2], with prevalence estimated to be between 2% and 4% by 65 years, increasing to 15% at 80 years of age[3] . In Europe, it is estimated that approximately 10 million people are affected, with costs of dementia projected to exceed €250bn by 2030 (Cimler et al., 2019). In the absence of effective pharmacological treatment to curtail or reverse the mechanisms underlying age-related cognitive decline, it is necessary to shift focus towards methods of prevention, with lifestyle approaches representing a promising avenue for further development.

The link between nutrition and cognitive decline has been the focus of ILSI Europe's events on 'Nutrition for the Ageing Brain' since the first successful meeting took place in 2014. ILSI Europe's events on 'Nutrition for the Ageing Brain' provide a forum for discussion of complex issues relating to nutrition and brain ageing science, bringing together experts from areas of food science, nutrition, developmental ageing, and cognitive science. These events have resulted in high quality and impact peer-reviewed publications (Miquel et al., 2018; Vauzour et al., 2017). Previous events have focused on the mechanisms of ageing and their interactions with nutrients (Miquel et al., 2018; Vauzour et al., 2017). The focus of the 2018 symposium held in Madrid has shifted towards clinical and applicable aspects of what we know so far regarding the impact of nutrition on maintaining brain health with age. This overview summarises the main themes discussed during this most recent ILSI Europe event, enlarged with the current state of knowledge on how nutrition influences healthy ageing. Topics discussed include biomarkers of nutrition, the role of the gut microbiome, new avenues for research, and recommendations regarding how the critical field of nutrition and neurodegeneration research should move forward into the future.

2. Nutrition for healthy ageing

The brain undergoes neural development until approximately the age of 30 years (Lebel and Beaulieu, 2011; Sowell et al., 2003; Westlye et al., 2010), after which a slow process of atrophy takes place, with clinical signs of neurodegeneration typically not occurring until older age. This trajectory is proposed to be determined by a complex interplay of genetic, endogenous and environmental factors (Livingston et al., 2017). The typically slow nature of this process allows for a significant window of opportunity for preventive intervention strategies. Nutrition has been identified as one promising avenue reducing the risk for age-related pathologies such as age-related neurodegeneration and dementia.

Nutritional epidemiology has suggested a protective role of healthy diets and of several candidate nutrients for brain aging outcomes. Existing evidence suggests that some nutrients or food ingredients, in particular specific vitamins, flavonoids and long chain ω-3 fatty acids have a potential to beneficially affect cognitive function (Samieri, 2018; Scarmeas et al., 2018). Beyond a focus on specific nutrients, the most optimal preventative avenues are suspected to be based on multi-nutrient approaches, as suggested by findings from the Three City observational study (Amadieu et al., 2017) and other cohort studies (Berti et al., 2015; Bowman et al., 2012; Gu et al., 2016; Lehtisalo et al., 2019; Olde Rikkert et al., 2015; Soininen et al., 2017), whole diet approaches, as well as multi-domain approaches incorporating changes to nutrition amongst other lifestyle factors such as exercise (Lehtisalo et al., 2019; Ngandu et al., 2015; Scarmeas et al., 2018). Indeed, several recent observational and intervention studies have incorporated approaches of specific nutrients, such as the VITACOG trial (Oulhaj et al., 2016) which focused on the efficacy of B vitamins to lower biomarkers related to cognitive decline including homocysteine, combinations of nutrients, such as the LipiDiDiet (Soininen et al., 2017), whole diet approaches, such as with the HELIAD study (Anastasiou et al., 2018) which investigate adherence to a Mediterranean dietary pattern and brain health. These multi-nutrient approaches highlight specific nutrients impacting brain ageing.

2.1. Specific nutrients

2.1.1. B-Vitamins

Studies in the USA and in Europe have found that higher intakes of B vitamins, particularly folates but not B12, were associated with lower risk of dementia or Alzheimer's disease (AD); e.g. the Baltimore Longitudinal Study of Aging (Corrada et al., 2005), and the Three City study (Lefevre-Arbogast et al., 2016). The Three City study was a longitudinal population-based study which focused on associations between the risk of age-related cognitive decline and dementia and vascular factors in a total of 9294 older adults aged 65–79 years (Antoniak et al., 2003). In addition to assessment of vascular risk factors, this study also involved extensive dietary, cognitive, and laboratory investigations. Notably, results from this study indicated that higher intakes of B vitamins, particularly folates but not B12, were associated with lower dementia risk (Lefevre-Arbogast et al., 2016). Further evidence suggests that combination of low folates and low B12 relates to higher circulating levels of homocysteine, such that plasma total homocysteine is sensitive and reliable biomarker of folate and vitamin B12 status (Refsum et al., 2004). Raised plasma homocysteine has itself been associated in prospective studies with increased risk of cognitive decline and dementia (Smith and Refsum, 2016; Smith et al., 2018), brain atrophy (Smith and Refsum, 2016), and AD pathology (Hooshmand et al., 2013). However, direct relationships between levels of folate and B12 and brain health are less consistent in the literature and yet to be firmly established (Smith, 2008). To further investigate the association between these B vitamins, homocysteine and cognitive

[2] World Alzheimer Report 2018.

[3] World Alzheimer Report 2015: The Global Impact of Dementia.

decline, the VITACOG study recruited 270 community-dwelling subjects > 70 years old with mild cognitive impairment (MCI) and randomised participants to either a daily placebo or tablet containing 0.8 mg folic acid, 0.5 mg B12, and 20 mg B6 over two years (Smith et al., 2010). Following treatment, the degree of brain atrophy as measured using structural magnetic resonance imaging (MRI) was reduced by 30% in the group receiving the B vitamins. There was further attenuation of atrophy in key grey matter regions including the medial temporal lobes in the active treatment group, with regional grey matter loss of 0.6% compared to 5.2% in the placebo group (Douaud et al., 2013). Regarding the association with homocysteine, total brain atrophy in the placebo group doubled across the levels of baseline homocysteine, whereas in the active treatment group there was no relation between homocysteine at baseline and atrophy, such that subjects within the top quartile of homocysteine levels showed a 53% slowing of the rate of brain atrophy (Smith et al., 2010). Furthermore, subjects receiving B vitamins showed a slower rate of decline in episodic memory, semantic memory and global cognition as measured by the Mini-Mental State Examination (MMSE), but only in subjects with baseline homocysteine levels above the median (> 11 μmol/L), and improvements in clinical and functional outcomes occurred in subjects with higher baseline homocysteine levels (> 13μmol/L) (de Jager et al., 2012). These findings suggested that the disease mechanisms underlying MCI and subsequent cognitive and clinical aspects could be modified by B vitamins, in particular for those with elevated levels of homocysteine (Smith and Refsum, 2017). Other trials in which B vitamins were administered have also shown beneficial effects on cognition, but some trials have not shown benefit; possible reasons for these discrepancies have been discussed (McCaddon and Miller, 2015; Smith and Refsum, 2016; Smith et al., 2018). In particular, a meta-analysis (Clarke et al., 2014) claimed that there was no beneficial effect of B vitamins on 'cognitive ageing' but this analysis is difficult to interpret since cognition was only tested on one occasion in 74% of the participants and so cognitive decline over time could not be assessed in these subjects. One reason why some B vitamin trials appear to have failed was revealed in the VITACOG trial, where it was found that only those participants with a good omega-3 fatty acids status benefitted from B vitamin treatment (see Section 2.2).

2.1.2. Other vitamins and nutrients

Other vitamins and nutrients have been identified as potential candidates for improving brain ageing however with far less weight and consistency of supporting evidence. For example, evidence suggests that a deficiency in vitamin D (25(OH)D < 25 nmol/L (10 ng/mL)) is related to risk of dementia (Feart et al., 2017; Jayedi et al., 2018), although null findings have also been reported in two large cohorts, the Framingham Heart Study (Karakis et al., 2016) and the Uppsala Longitudinal Study of Adult men (Olsson et al., 2017). In addition, vitamin E, specifically γ-tocopherol (but not α-tocopherol) has been associated with lower levels of AD pathology in the human brain (Morris et al., 2015a), however there still remain very few biomarker studies on this nutrient and its role in brain health remains controversial (Scarmeas et al., 2018). Likewise, studies on carotenoids have been generally limited to dietary questionnaires to assess exposure (Cho et al., 2018; Li et al., 2012). Even if plasma carotenoids were found to significantly relate to lower dementia risk (Feart et al., 2015), further biomarker investigations are again rare and some investigations haven't found a link with risk of cognitive change. For example, the Nurse's health study (Kang and Grodstein, 2008) found no association of plasma carotenoids with cognitive change.

Many trials suffer from insufficient samples sizes and duration, which may contribute to the inconsistency in findings. A recent systematic review of 38 trials of nutrient supplementation which included omega-3 fatty acids, B vitamins, vitamin D and carotenoids, concluded that no evidence-based recommendations can be made for the efficacy of over the counter vitamin supplements to protect against cognitive decline in cognitively healthy adults or those diagnosed with MCI (Butler et al., 2018), but this review did not take into account the analysis of subgroups that was shown to be crucial in the VITACOG trial (see above).

2.1.3. Omega-3 fatty acids

Omega-3 fatty acids have received considerable attention in the context of nutrition and ageing particularly regarding their possible role in reducing the risk of age-related cognitive decline. Indeed, observational studies such as the Three City Study showed that higher blood levels of the long-chain omega-3 fatty acid eicosapentaenoic acid (EPA) were associated with lower dementia risk and less atrophy of the medial temporal lobe (Samieri et al., 2008, 2012) (whereas blood levels of docosahexaenoic acid (DHA) did not reach a significant association with dementia outcomes in these studies). However, with regards to pathological age-related decline specifically, there have been findings of higher blood levels of DHA to be associated with lower dementia risk (Zhang et al., 2016). A meta-analysis showed that observational studies support a favourable association between intake/blood levels of DHA (alone or combined with EPA) with memory function in older adults with mild memory complaints (Yurko-Mauro et al., 2015).

But randomised-controlled trials (RCT) failed so far to show positive effects of omega-3 fatty acids supplementation on cognitive performance in cognitively healthy older subjects (van de Rest et al., 2008), or on cognitive decline in elderly people with memory complaints (Multidomain Alzheimer Preventive Trial (MAPT) (Andrieu et al., 2017)). The DHA dose used in the MAPT (800 mg/day) is below the maximum recommended daily intake and even higher doses (above 1 g) showed negative results on cognitive outcomes in trials for MCI and mild AD probably because the brain pathology is already well advanced in those patients (Yassine and Schneider, 2017). Therefore omega-3 supplementation might better be tested for prevention purposes in patients with early dementia (prodromal stages) in trials with larger sample size and for longer periods to ensure that the intervention has a chance for success. Indeed, findings from a previous meta-analysis have hinted that the positive effects of omega-3 supplementation on cognitive performance could be limited to specific cognitive domains in milder cognitive impairment in the absence of dementia (Mazereeuw et al., 2012).

Such inconsistency in findings could in part be due to the challenges relating to measuring habitual intake based on biomarkers of nutrients not consumed on a daily basis (i.e. marine long-chain omega-3 fatty acids) using a single blood draw; and in part to factors such as large variability in composition of bioactives within the same type of food source; and individual differences in rates of nutrient metabolism. Another possible reason for inconsistency is that omega-3 fatty acids may need to interact with other nutrients in order to have a beneficial effect; for example, there is evidence of interaction with B vitamins, as discussed thereafter.

2.2. Multi-nutrient interventions

Beyond the impact of specific nutrients working in isolation to improve health, more attention is now being directed towards identifying combinations of specific nutrients to protect against cognitive decline. Indeed, combinations of nutrients, specifically between fatty acids, vitamins A, E, and D, and carotenoids, have been identified as a candidate pattern of nutrients relating to long-term risk of dementia in healthy older adults (Amadieu et al., 2017). Specifically, a pattern consisting of low levels of vitamin D, carotenoids and polyunsaturated fatty acids in conjunction with high levels of saturated fats was associated with a 3.7 fold higher risk of dementia onset – twice the risk conferred by carrying the *APOEε4* genotype (Amadieu et al., 2017). However, these findings require further replication, as previous studies have been predominantly cross-sectional and limited, and the role of B vitamins in combination with other nutrients has yet to be adequately investigated.

Post-hoc results from the VITACOG study showed that levels of total plasma omega-3 fatty acids modulated the impact of the B vitamin treatment with respect to slowing brain atrophy (Jerneren et al., 2015) and cognitive and clinical outcomes (Oulhaj et al., 2016), suggesting that indeed the effect of B vitamins on brain health may depend on larger dietary patterns involving other key nutrients. Likewise, the beneficial effect of omega-3 fatty acids may depend upon B vitamin status. The OmegAD trial, a single-centre randomized control trial which primarily investigated the effect of supplementing omega-3 fatty acids on measures of cognition in 204 patients with mild to moderate AD, found in a recent post-hoc analysis that omega-3 fatty acids improved cognition in AD only in a subgroup with good B vitamin status as revealed by low levels of the marker homocysteine despite not finding an impact on slowing cognitive decline across the whole cohort (Jerneren et al., 2019), suggesting that an interaction between concurrently higher omega-3 fatty acids and B vitamins could be more critical for preventing cognitive decline.

The LipiDiDiet (Soininen et al., 2017) is one of the very few existing interventions involving a multi-nutrient approach. This double-blind, placebo-controlled multicentre trial investigated the impact of a combined supplement Fortasyn Connect (Souvenaid®) consisting of 11 nutrients linked previously to brain health (uridine monophosphate, choline, phospholipids, EPA, DHA, vitamins E, C, B6, B9, B12, and Selenium), in 311 adults with prodromal AD (Soininen et al., 2017) taken over 24 months. Although the study found that in the control population the cognitive decline was less than expected and thus the primary endpoint (a Neuropsychological Test Battery) was inadequately powered, the intervention produced significant benefits on clinical measures on cognitive performance and everyday function. Regarding biomarkers, the intervention resulted in significantly reduced brain atrophy, particularly in hippocampal and ventricular regions, and further evidence for effects mediated via biomarkers such as homocysteine and DHA status. The benefit of this intervention appeared further to be modified depending on how early in the disease process treatment had been initiated. These results suggest that this particular combined nutrient intervention could slow disease progression when taken over an extended period of time. Despite these promising findings, optimal combinations of specific nutrients that stop disease progression or which are more effective at the dementia stage of the disease have yet to be determined.

2.3. Whole diet approaches

Due to complex interactions between nutrients and foods, the use of a whole-diet approach may provide advantages in understanding the role of diet and cognitive impairment. Thus, adherence to dietary patterns has been evaluated in many investigations. The candidate nutrients for prolonging brain health with age are found abundantly in certain whole-diet approaches. In particular, the Mediterranean diet, which has been the most extensively studied dietary pattern in the context of brain ageing as well as other health conditions such as heart disease and cancer (Dinu et al., 2018; Trichopoulou, 2004). The Mediterranean diet originates from the food cultures around the Mediterranean Basin (Davis et al., 2015). Although several variants of the Mediterranean diet exist, it is generally characterized by abundance of plant foods including fruits (an after-dinner dessert or a between-meal snack), vegetables (as either main or side dish), bread and other forms of cereals, legumes, nuts, and seeds. Olive oil is the principal source of fat. The Mediterranean diet also includes moderate amounts of dairy products (principally the fermented ones, i.e. cheese and yogurt), low to moderate amounts of fish and poultry, red meat in low amounts and wine, consumed modestly, normally with meals. Evidence from longitudinal studies and clinical trials indicates that adherence to the Mediterranean diet is associated with slower rates of decline in cognitive performance and with lower risk for cognitive impairment (Scarmeas et al., 2018; van den Brink et al., 2019).

One of the most prevalent studies investigating the impact of a Mediterranean style diet on health outcomes was the PREDIMED (Prevención con Dieta Mediterránea) study (Estruch et al., 2018), which was a multicentre trial conducted in Spain focusing mainly on older adults (55–80 years) who had high cardiovascular risk from May 2005 to December 2010. Participants were allocated to either a Mediterranean-style diet with extra-virgin olive oil, a Mediterranean-style diet with mixed nuts, or a control diet that focused on limiting overall dietary fat intake. Particularly, one finding from this study relevant to the current discussion was that a Mediterranean diet with extra-virgin olive oil was associated with higher scores of global cognitive performance following the 6.5 year nutritional intervention (Martinez-Lapiscina et al., 2013). Similarly, the NU-AGE study ("New dietary strategies addressing the specific needs of elderly population for healthy ageing in Europe") (Santoro et al., 2014) was a 12-month dietary intervention conducted between May 2011 until April 2016 which sought to modulate the deleterious effects of chronic inflammation and other age-related disease processes in a total of 1250 older adults (aged 65–79) by implementing a personally-tailored Mediterranean-style diet intervention. The study took place in centres in France, Italy, the United Kingdom, the Netherlands and Poland. Although results relevant to the main objectives of the study are still being processed, available results show that a higher adherence to the Mediterranean diet over the year-long intervention was associated with statistically significant improvements in overall cognition and measures of episodic memory compared with participants with lower adherence (Marseglia et al., 2018), despite a general good uptake of the diet across the different European regions (Berendsen et al., 2018).

Currently, the HELIAD study is a population-based multidisciplinary study on the prevalence of ageing-related neuropsychiatric conditions and the potential associations between diet, lifestyle and cognitive performance in older adults (Dardiotis et al., 2014). Study participants were randomly selected from community-dwelling adults over the age of 65 years from two municipalities in Greece, Larissa (small urban centre) and Marousi (large urban center). Information pertaining to demographics, medical history, neurological and psychiatric assessment of the participants, including a comprehensive neuropsychological evaluation of all major cognitive domains was collected in addition to dietary and lifestyle habits, such as sleep, physical activity, and social interaction. A cross-sectional analysis of the 1864 participants showed a positive association between adherence to the Mediterranean diet and a decreased risk for dementia, as well as better cognitive performance in multiple domains including memory (Anastasiou et al., 2017). In addition, adherence to a lifestyle index incorporating factors such as sleep, physical activity, and involvement in activities of daily living showed higher adherence to these lifestyle factors was related to better cognitive function (Anastasiou et al., 2018). These findings suggest that a multi-domain approach incorporating diet alongside other health-promoting lifestyle factors could optimize beneficial effects on promotion of cognitive performance and prevention of decline with age. Indeed, trials such as the FINGER (Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability) study emerged to investigate the impact of a 24-month multi-domain approach to preventing cognitive decline in older at-risk individuals aged > 60 years (Ngandu et al., 2015). The FINGER trial has been the first large longitudinal randomized control trial which involves a combination of exercise, diet, cognitive training and management of vascular risk factors. This trial has produced promising results regarding the impact of the multidomain intervention on overall cognitive outcomes compared to the control group, however the individual impact of each of the intervention components remains to be elucidated and which lifestyle changes or combination thereof are effective at delaying cognitive decline.

Despite these promising findings in support of the Mediterranean diet as a beneficial approach to preventing age-related cognitive decline, the evidence remains limited and further investigation is

required. In particular, evidence from carefully designed prospective studies with long follow-up periods and conclusive intervention trials is needed. Regarding the diet itself, many aspects of the diet such as fluid intake, timing, distribution of food intake during the day and behaviours associated with eating have not yet been evaluated. The mechanisms by which this dietary pattern exerts its beneficial effects on health also remain to be fully elucidated. This is particularly relevant for populations which may have different genetic and epigenetic variations, gut bacterial diversity, and variation in metabolic status and exposure to environmental factors, as these aspects could significantly modulate the impact of dietary interventions on health outcomes. There is, however, evidence of the possible beneficial effects of the Mediterranean diet in the USA (Scarmeas et al., 2006) and of a modified Mediterranean diet, the MIND (Mediterranean-DASH Intervention for Neurodegenerative Delay) diet (Morris et al., 2015b, c). The MIND diet combines principles from the Mediterranean diet and the DASH (Dietary Approaches to Stop Hypertension) diet, aiming at reducing dementia and a decline in brain health. Importantly, the first clinical trials designed to test the effects of a 3-year intervention of the MIND diet on cognitive decline among older subjects are ongoing.

To optimize the impact of these interventions on prevention of age-related cognitive decline, lifelong environmental and genetic components which increase vulnerability to neurodegeneration need to be further identified and understood, and possibly incorporated as additional targets in future interventions towards a more personalized approach to nutrition. Indeed, there is a growing interest in other factors that could modulate the impact of these interventions, with one of the most salient being the influence of the gut microbiome on disease processes related to neurodegeneration, which remains a very open field. This potential modulating role of the microbiome and its relevance to nutrition and the ageing brain will be explored further in the next section. The exploration of these modulating factors requires accurate methods and models in order to assess efficacy of future interventions, which will be explored further in the next section.

3. New research avenues

3.1. Microbiome: impact on the ageing brain

Many age-related diseases, including neurodegenerative conditions, are considered to be the result of a complex interaction of disease processes involving the immune system, inflammation, and recently the microbiome. The gut microbiome is the collective genome underlying the 10^{13}-10^{14} microorganisms which make up the gastrointestinal microbiota, predominantly bacteria but also including fungi, viruses, and other single-celled organisms (Montalban-Arques et al., 2015). The human gut microbiome is being increasingly recognized as a potent physiological contributor to health. The structure of the gut microbiome varies considerably between individuals, as well as within individuals over the lifespan, in response to both endogenous and environmental factors, including host genetics, age, diet, lifestyle and disease.

With specific regard to age, the gut microbiome undergoes significant changes across the lifespan, featuring hallmark characteristics in the different phases of life (Cani, 2018; Kundu et al., 2017). The ageing process is characterized by several disease-causing mechanisms which could be influenced by changes to the gut microbiome. Such processes include: 1) cellular ageing, including oxidative damage, telomere shortening, advanced glycation end products (AGEs) formations, damage to DNA; 2) immunosenescence, including changes in adaptive immunity such as the reduced ability to produce new antibodies and poor vaccine response, and inflammageing, altered innate immunity, such as reduced activity of “killer” cells and chronic systemic inflammation with elevated IL-6, CRP and TNF-α; 3) changes in body composition, including reductions in muscle mass and increased adiposity; 4) changes in gut physiology, including the type and quality of intestinal mucin produced, changes in gut permeability, reduced transit times, increased *Helicobacter pylori* carriage and small bowel bacterial overgrowth (SBO); and 5) dysregulation of tryptophan metabolism, particularly via kynurenine pathways, resulting in levels of bioavailable serotonin which has been linked to a number of neurodegenerative conditions including dementia (Ruddick et al., 2006; Schwarcz et al., 2012), which in turn could be regulated by gut microbiota composition (Clarke et al., 2013; Desbonnet et al., 2008; Wikoff et al., 2009).

As such, older age is generally associated with an aberrant gastrointestinal microbiome profile characterized by modified microbiome resilience and loss of homeostatic regulation of microbial diversity, enrichment in pathogenic bacterial species and rearrangements in saccharolytic and proteolytic microbial populations (Kelly et al., 2015; Qin and Wade, 2017), with especially a reduction in short-chain fatty acid (SCFA) producers (Biagi et al., 2017). One of the pioneering studies in the field, Claesson et al. (Claesson et al., 2012), demonstrated that the gut microbiota changes in the elderly are closely related to the host health and residential status. Interestingly however, de la Cuesta-Zuluaga et al. (2019) demonstrated that the influence of the host’s sex decreases over the lifespan, such that greater bacterial diversity was detected in younger women than men but this difference was not significant after middle age (de la Cuesta-Zuluaga et al., 2019). Indeed, while the microbial populations detected in community-dwelling healthy elderly are overall comparable to those of young adults, elderly living in long-term residential care and frail elderly bear a distinct, “more” compromised microbiome signature, with low biodiversity, underrepresentation of SCFA-producing bacteria and low fecal levels of SCFAs, possibly contributing to the age-related functional decline.

Biagi et al. (Biagi et al., 2016) reconstructed the longest available trajectory of the human gut microbiome along ageing, from young adults up to the extremes of human lifespan, i.e. centenarians and semi-supercentenarians (persons who reach the age of 105 years). Confirming previous findings, the authors observed a core microbiota of symbiotic bacterial groups (mainly SCFA producers) with diversity and cumulative abundance decreasing along with age, and an age-related increasing contribution of opportunistic and allochthonous bacteria. Interestingly, the gut microbiota of extremely old people showed some peculiarities, including the presence of microorganisms typical of other niches (e.g. *Mogibacteriaceae*, known to be abundant in the periodontal environment) and the enrichment and/or higher prevalence of health-associated taxa: *Bifidobacterium* (well-known probiotics with long history of use), *Akkermansia* (recently proposed as next-generation probiotics or live biotherapeutics for the treatment of obesity and related complications) (Cani and de Vos, 2017; O’Toole et al., 2017) and *Christensenellaceae* (whose relative abundance has been found to be significantly influenced by host genetics (Goodrich et al., 2014)). This provided the fascinating glimpse of a possible biological print of ageing-supportive/longevity-adapted microbial communities. Indeed recent findings suggest that human age can be predicted based on individual microbial profiles and that such features selected by predictive models are age-related (Galkin et al., 2018).

From a functional point of view, Rampelli et al. (Rampelli et al., 2013) found a distinctive microbiome structure in Italian centenarians, with an overall proteolytic propensity matching the observed alterations in urinary and serum levels of aromatic amino acids and their metabolites (Collino et al., 2013). It is worth noting that the centenarian gut metagenome also harboured features that are known to support longevity in experimental models: i) reduced folate synthesis and ii) increased biosynthesis of polyamines. The comparison of microbiota data from Italian centenarians to those from China and Japan revealed common features, including the decrease in SCFA producers and the enrichment in pathobionts as well as in health-associated taxa, which could represent robust, universal signatures of longevity (Santoro et al., 2018). Of course, it is impossible to know if the health-associated features of the centenarian microbiome were already present at a younger age, (re)acquired later on or somewhat related to the

individual's past life. Similarly, it remains to be determined whether the microbial shifts during the human lifetime merely reflect secondary biological changes or are the result of an adaptive process and contribute to age-related physiological transitions. Promising findings from animal models emphasize the lifelong value of commensal bacteria (and derived compounds) to their host (Han et al., 2017) but we are still far from knowing if these microbiota roles in animal longevity also impact humans and, above all, if they can be manipulated. In an attempt to provide answers to at least some of these questions, lifelong longitudinal studies or continuation of existing ones to follow microbial changes within the same individual across life should be promoted. Future research should also combine metagenomics with other fields, including meta-transcriptomics and metabolomics, as well as with "culturomics" and animal models, to improve understanding of the intricate microbiome-host crosstalk and the relationships between specific microbial communities and their products and age-dependent phenotypes.

Even though several questions are still unanswered, overall the available findings suggest that manipulating the gut microbiome towards a healthy-like/ageing-supportive profile (e.g. through diet, physical activity, administration of probiotics and/or postbiotics, or even faecal microbiota transplantation) could be an effective way to activate major host longevity signalling and promote healthy ageing. In particular, the growing recognition that microbiota could play a key role in the functioning of the gut-brain axis could reveal a key role of microbiota in promoting brain health with age and preventing neurodegeneration. The mechanisms by which microbiota could influence the functioning of the brain appear to be complex and multidirectional, involving neural, endocrine and immune pathways. Of particular importance in the context of the role of gut microbiota in supporting brain function over time is whether these pathways could be modulated via dietary impacts on gut microbiota, revealing the possibility to curtail age-related neurodegeneration through dietary changes.

3.2. Prebiotics, probiotics and postbiotics

The growing focus on the human gut microbiome as an avenue to maintain brain health, has also nurtured interest in prebiotics both as tools to discern the mechanisms underlying microbiome-gut-brain axis communication, and as interventions to assist in the treatment of mental illnesses. According to the latest definition by the International Scientific Association of Probiotics and Prebiotics (ISAPP), dietary prebiotics are defined as 'a substrate that is selectively utilized by host microorganisms conferring a health benefit' (Gibson et al., 2017). Prebiotics include dietary fibers that facilitate the growth of beneficial gut bacteria and have been suggested to influence neurobiology and behavior through an impact on gut microbiota. Regarding specific prebiotics, studies involving the commercially available galacto-oligosaccharide prebiotic (B-GOS) have shown increased growth of *Bifidobacteria* compared to a fructo-oligosaccharide (FOS) prebiotic. In rodents, this effect is further associated with the prevention of post-inflammatory anxiety (Savignac et al., 2016) and improvement in cognitive flexibility (Gronier et al., 2018). In human studies, B-GOS prebiotics have been shown to increase attentional vigilance to positive stimuli (Schmidt et al., 2015), similar to antidepressants. The pro-cognitive effect of the B-GOS prebiotic has now been demonstrated in schizophrenia patients who display severe cognitive deficits that are not alleviated by current treatments (Kao et al., 2019b).

The mechanisms of prebiotic actions on the brain remain elusive. The three main mechanisms that are currently considered to play a role in communication along the microbiota-gut-brain axis are 1) the immune system, 2) metabolites from the diet that result from bacterial fermentation, and 3) the vagus nerve connecting the gut to the brain. One particular suggested mechanism to underpin the central actions of prebiotics may involve acetate generated from their fermentation by the enteric bacteria. Acetate has epigenetic effects in the brain and modulates key glutamate receptors that are integral to neurodevelopment and cognition (Gronier et al., 2018). However, although acetate is readily absorbed and reaches the brain via the circulation, it is not solely responsible for the central effects observed after prebiotic ingestion (Kao et al., 2019a). Other possible mechanisms, through which SCFA's affect the brain, are the modulation of the vagus nerve activity, and/or through anti-inflammatory effects within the gut. In the latter instance, certain bacterial metabolites have been proposed to modulate the gut epigenome and permeability (Qin et al., 2018), which in turn impacts the infiltration and activity of immune cells as well as the absorption of bioactives and hormones (Postler and Ghosh, 2017; Qin et al., 2018). All these factors working individually or in synergy have the potential to impact on central function (Sarkar et al., 2016). There is no doubt that bacterial fermentation of prebiotic intake generates SCFA's, acetate, propionate and butyrate in the gut, but it is not clear how they contribute, if at all, to the psychotropic actions of these carbohydrates. An improved understanding of the mechanisms underlying the actions of certain prebiotics will identify pathways that could potentially be more effectively manipulated in order to treat brain disorders at all ages. Furthermore, since prebiotics occur naturally in the diet, knowing how they affect the brain, both in its healthy and disordered form, will provide useful information for healthy dietary choices.

In addition to escalating research into the mechanisms underlying the psychotropic effects of prebiotics, it is crucial that more human studies are conducted. Laboratory animals have fixed diets, and so prebiotic supplementation is more likely to have a robust and reproducible impact on microbial communities and gut physiology. Furthermore, replication of the positive cognitive effects seen following prebiotic intervention in schizophrenia (Kao et al., 2019b) are needed using other formulations and in clinical trials. These investigations should also be extended to other cognitive disorders such as dementia, and natural age-related cognitive decline. In all cases, prebiotics if proven effective at attenuating psychological symptoms of brain disorders are likely to be used adjunctively rather than on their own. That is, it is unlikely that manipulating the gut microbiome through the ingestion of a prebiotics alone will have an effect on central dysfunctions. It is more likely that supplements will be used as an additional therapy to improve brain metabolism and assist it in its response to current therapies.

Introducing beneficial bacterial species, such as *Bifidobacterium bifidum*, a probiotic (i.e. a live microorganism that when ingested confers positive health effects to the host), or adding prebiotics, such as fructooligosaccharides (FOS) promoting growth and activity of certain bacterial species are the conventional methods for manipulating the intestinal microbial community. Advances in high-throughput sequencing and metabolomics, however, have unravelled the importance of emerging postbiotics, which can be used to directly and specifically manipulate microbiota function (Wegh et al., 2019). The term "postbiotics" indicates any soluble factor resulting from the metabolic activity of a live bacteria or any released molecule capable of providing health benefits through a direct or indirect mechanism. There is substantial evidence to suggest that many health beneficial effects associated with the establishment of a symbiotic gut microbiota are promoted by bacterial metabolic by-products, although the role of specific bioactive compounds and their probiotic effects and how they are mediated by other metabolites remains to be elucidated and has not yet been adequately explored in humans. Particularly, there is a focus on the subgroup of probiotics commonly referred to as 'psychobiotics' which have direct influences on neural health via the release of neuroactive compounds via the gut-bacteria-brain axis (for review, see (Oleskin and Shenderov, 2019). Relevant to neurobiology of neurodegeneration and cognitive defects, identification of novel postbiotics and the pathways responsible for their production may improve mechanistic understanding of the role that specific probiotics, prebiotics, and postbiotics have in restoring intestinal microbiota composition and

associated neuroprotective functions (Mosca et al., 2019; Oleskin and Shenderov, 2019).

3.3. Improved biomarkers of diet and ageing

Metabolomics is a versatile tool that has many applications in nutrition research. Applications are wide ranging and include identification of dietary biomarkers, examination of mechanisms through which diet impacts on health and the study of diet related diseases. Metabolomics is the measurement of small molecules called metabolites in biological samples such as urine and blood. The main technologies used are Nuclear Magnetic Resonance (NMR) and Mass Spectrometry (MS) based approaches. NMR is a robust, reproducible, quantitative and high-throughput approach. However, it is not as sensitive as the MS based approaches. To achieve optimal coverage of the metabolome one should use multiple platforms.

With respect to the area of dietary biomarkers there is an urgent need for objective measures of dietary intake to be used in conjunction with self-reported dietary data. Metabolomic based approaches have been very successful in identification of new dietary biomarkers and published examples demonstrate that for certain foods quantitative analysis of the biomarkers can give an estimation of intake of the specific food. Furthermore, the work demonstrated good agreement between the biomarker data and intake as assessed by semi-weighed food diaries (Gibbons et al., 2017). Other examples of quantitative biomarkers are also available in the literature (Garcia-Perez et al., 2017). However, not all dietary biomarkers will deliver quantitative information with respect to food intake. However, these biomarkers are still very useful for studying relationships with health and disease. For example, 22 lipid biomarkers which were related to total dietary fat intake have previously been identified. From this panel a number of lipids demonstrated responsiveness to different levels of fat intake in an intervention study and importantly were related to HOMA-IR, a measure of insulin resistance. A recent study examining the relationships between circulating metabolites and cognition and dementia revealed that 15 metabolites were consistently associated with cognition across multiple cohorts (van der Lee et al., 2018).

While a number of putative biomarkers for food intake exist in the literature there is an urgent need to validate these against agreed criteria (Dragsted et al., 2018). Such criteria include biological plausibility, dose response studies and replication. Using these suggested criteria more work is needed to validate existing markers so that we are at a stage where we can have biomarkers that assess the major food groups and obtain a good assessment of dietary intake. In the field of cognitive health there is a lack of studies examining the relationship between circulating metabolites and cognitive health. Additionally, there is a knowledge gap with respect to the impact of cognitive decline on key metabolic pathways. Future research should investigate the underlying mechanisms for the observed associations between metabolites and cognition/dementia. Work should also examine if these metabolites could be used as a signature for prevention/therapeutic strategies. Furthermore, it would be worth investigating if modulation of these metabolites could be achieved through an intervention and if this in turn impacts on cognitive health. Future work should be devoted to developing biomarkers of food intake that in turn could be used to examine the relationship between food intake and cognitive health. Finally, cross collaboration between nutrition scientists and clinicians is crucial to maximise potential in this area.

Biomarkers of ageing help identify individuals at high risk of premature ageing. These biomarkers also shorten the period necessary to test the efficacy of preventive interventions aimed at promoting healthy ageing. Nine hallmarks of ageing were listed in 2013 (Lopez-Otin et al., 2013). This prompted a list of molecular, functional, and anthropometric parameters that change with chronological age and which therefore could be called biomarkers of ageing (Burkle et al., 2015). However, a single robust, universal, safe, and non-expensive biomarker of ageing remains to be identified. Although telomere length is discussed here, there exist other classes of biomarkers such as epigenomics and proteomics which are beyond the scope of this current review (for a more comprehensive review, see (Zierer et al., 2015).

Telomere attrition was listed as one the nine hallmarks of ageing (Lopez-Otin et al., 2013). Telomeres are repeating DNA sequences located at chromosomal ends that protect genomic stability. Telomeres shorten each time a somatic cell divides, and this fostered the use of telomere length in circulating cells as a biomarker of ageing in many epidemiologic studies. However, while telomere length is a good marker for proliferating cells (i.e. microglial cells), its validity for tracking replicative senescence of organs or tissues rich in post-mitotic cells (i.e. post-mitotic neurons) is still a matter of debate. Be it as it may, shorter telomeres are associated with a decreased life expectancy and increased rates of developing age-related chronic diseases. Focusing on brain, case-control studies have repeatedly reported that patients with AD display shorter telomeres compared to controls (Forero et al., 2016) and a causal link has been suggested through a Mendelian randomization approach (Zhan et al., 2015). However, the association is less firmly established in prospective studies on telomere length and cognitive decline (Zhan et al., 2018).

Oxidative stress and inflammation are believed to play a key role in brain ageing. On the other hand, both inflammation and oxidative stress also relate to telomere attrition, and observational studies reinforced the notion that long-term consumption of antioxidant-rich foods such as seeds, nuts and whole grains relate to preserved telomeres (Freitas-Simoes et al., 2018). It follows that sustained consumption of plant-based foods (i.e. rich in antioxidant and anti-inflammatory compounds) might delay brain ageing by counteracting telomere attrition. Nevertheless, research on this interplay is still in its infancy. In the framework of the Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER) trial, conducted in elderly people at risk for dementia (Ngandu et al., 2015), the cognitive benefits from the advice to increase consumption of plant foods as part of a multi-domain intervention over control (general health advice) were more pronounced in participants at the bottom tertile of baseline telomere length of circulating cells (so-called “higher-risk individuals (Sindi et al., 2017)”). This is a promising finding. However, a tentative telomere length cut-off point to identify individuals at high risk of cognitive decline (i.e. those who can obtain the largest cognitive benefits of lifestyle-related interventions) is yet to be established. In addition, further refining on the influence of age, risk of cognitive decline, dietary background, duration of supplementation, and type of supplementation (nutrient or bioactive *vs* food *vs* dietary pattern; alone *vs* multi-nutrient *vs* multi-domain) is warranted in long-term and adequately powered randomized controlled trials exploring the interplay between diet, telomeres and cognition. Cognitively healthy participants with genetic risk factors of AD appear as an ideal population to conduct such trials.

3.4. Brain metabolism

Brain PET imaging shows that deteriorating brain energy metabolism is a pre-symptomatic problem that increases the risk of AD in older people, individuals with insulin resistance, carriers of the *PSEN1* (presenilin 1) and *APOE4* (apolipoprotein E4) genetic mutations, and in people with a family history of AD (Cunnane et al., 2016). The deterioration of brain energy metabolism is specific to glucose – it does not affect the brain’s metabolism of ketone bodies in older people (Castellano et al., 2019), in MCI (Fortier et al., 2019) or in AD itself (Croteau et al., 2018). This is a crucial observation because it shows that brain cells having difficulty using glucose can still use ketones as an alternative energy source, indicating that the neurons are not completely lost, and also that brain energy rescue by ketones is a potential strategy to slow down the onset and possibly progression of AD.

Indeed, recent PET studies show that this ‘ketone rescue’ strategy

could provide benefits to brain metabolism (Fortier et al., 2019). A ketogenic drink containing medium chain triglyceride (MCT) reduces the brain energy gap caused by the brain glucose deficit in both MCI and AD in direct proportion to the plasma ketone level achieved. Furthermore, cognitive outcomes improve in MCI in direct relation to the plasma ketone level achieved by the MCT drink. This has been demonstrated in a 6-month randomized, placebo-controlled trial (n = 19–20/group; (Fortier et al., 2019). Based on these results, (i) deteriorating brain energy metabolism appears to be an early and a central issue in MCI and AD but it is a problem for which a ketogenic intervention (diet or drink) is a potential solution, (ii) nutritional (or pharmaceutical) approaches to treating MCI or AD are unlikely to achieve their full potential unless the problem of the brain energy (glucose) deficit is addressed. The implication is that a larger trial adequately powered for cognitive (not metabolic) outcomes is now warranted.

There remain however several unanswered questions relating to brain energy metabolism and the role of ketones being used as an energy source promoting cognitive health. The effective dose and trial duration required of such a MCT ketogenic drink to optimize benefits on cognitive outcomes remains to be determined. Finally, it should be investigated whether other approaches established to produce changes in brain energy metabolism, such as caffeine (Vandenberghe et al., 2017) or exercise (Castellano et al., 2017), should also be incorporated into such an intervention, or whether this intervention should be part of a multi-nutrient approach to mitigating neurodegenerative disease progression.

3.5. Novel brain models

The broad availability of human stem cells, especially of induced pluripotent stem cells (iPSC), has prompted the development of a number of human brain organoid models. They come with different advantages and disadvantages as to size, standardization, reflection of anatomy and physiology and costs. The use of iPSC allows using different genetic backgrounds or iPSC lines, which were genetically modified (isogenic cell lines), for example carrying certain risk or reporter genes. As the model reflects the developing brain, it has obvious uses for developmental neurotoxicity (Hartung et al., 2017; Pamies et al., 2018; Smirnova and Hartung, 2018), such as studies for causes and treatments of autism.

In the context of the ageing brain, a number of brain diseases of the elderly have been investigated using this approach. Based on the finding that Alzheimer patient's iPSC allow the generation of neurons showing some hallmarks of the disease (Israel et al., 2012; Muratore et al., 2014), such mini-brain models have started to be produced. Similarly, a number of iPSC lines from patients with amyotrophic lateral sclerosis have been employed to produce and compare the respective mini brains, which is currently expanded to a larger number of donors. Parkinson Disease is typically studied in animals treated with substances selectively destroying dopaminergic neurons but has since been successfully translated to mini-brain models using substances such as MPTP, its active metabolite MPP + or hydroxy-dopamine. In conclusion, a number of neurodegenerative diseases typically affecting the elderly can be modelled with brain and other organoid models derived from human stem cells. Altogether, the mini-brain models represent a versatile tool for brain research in various settings, allowing for research not previously possible with rodents, and allowing examination of disease models prior to clinical investigations in humans.

4. Shortcomings and future directions

There remain several significant shortcomings in nutrition research focusing on candidate nutrients or dietary patterns which need to be addressed in future investigations. A focus on improving the accuracy and validity of dietary biomarkers is required in order to quantify intake and measure change following a dietary intervention to establish dose-dependent causality between intake and health outcomes. Current estimates of dietary intake are dependent on food frequency questionnaires, which rely on published food composition data. In addition to limitations related to self-report instruments (Archer et al., 2013; Yuan et al., 2017), the high variability in food composition, for example even within fruit taken from the same plant (Kuhnle, 2018; Wilkinson and Perring, 1961), makes it very difficult to estimate intakes of certain nutrients from whole foods, and instead mean values of nutritive compounds are often taken to estimate dietary intakes. Methods of preparation of certain foods can also affect composition, for example the length of brewing time of tea can significant affect the availability of flavan-3-ols (Fernando and Soysa, 2015). Biochemical markers of dietary intake overcome the issues of imprecise measurement and variability in food composition, as they rely instead on compounds that have actually been extracted by the body (Kuhnle, 2012) (see section 1.3.5). As previously discussed, future research should continue to explore the utility of biomarkers whilst ensuring that their use is validated against up-to-date published criteria.

Previous studies investigating the impact of specific nutrients or combinations of nutrients on health may not have adequately targeted populations that would benefit most from these interventions. Subjects that have sufficient or high levels of certain nutrients at baseline may not benefit in the same way from these approaches as those who are deficient or have lower levels of candidate nutrients, and as such results from studies grouping people regardless of baseline status may lead to milder and non-significant associations. Furthermore, targeting older adults in the prodromal stages of neurodegeneration, when they may be more susceptible to prevention approaches, could produce more robust results compared to focusing on healthy older adults or individuals living with more pronounced conditions where the stage of atrophy within the brain does not allow for significant improvements to be observed. It may be possible to identify an optimal intervention time point or window or set of conditions where benefits are most likely to be observed. Clinical trials are continually aiming to target earlier stages in the disease process to maximise benefits, which corresponds with improvements in detection of disease leading to earlier diagnosis. However, it remains unclear how early in the disease process treatment would be feasible.

It is prudent to acknowledge that there is increasing concern regarding the selection of valid, reliable and sensitive cognitive and neuropsychological assessments and the associated practice and procedures utilized to assess nutritional effects on the ageing brain. Some authors have drawn attention to growing distrust of the findings emanating from industry-academia collaborations (Fabbri et al., 2017; Katan, 2007; Lesser et al., 2007; Nestle, 2016). The research community needs to address these concerns and ensure the integrity of the research outputs. There are clear indications of data dredging and p-hacking (Simmons et al., 2011), which are particularly relevant to neuropsychological tests where there are often multiple outcome measures for individual tests (e.g. speed of response, accuracy). Numerous strategies have been employed to analyse these outcomes and some authors combine individual test outcomes into factor scores or composite measures of a purported cognitive domain which could increase the likelihood of a significant effect. The ease with which computerized cognitive batteries can now be designed and implemented is contributing to greater diversity in measures of cognition, and therefore, reduced standardization of procedures. This reduces comparability of findings between studies, which can give the impression of lack of coherent effects. There is an obvious way to tackle these concerns; increase replication and address the so-called reproducibility crisis (Maxwell et al., 2015; Sorkin et al., 2016). However, this is hampered by the pressure to attain to novel, marketable outcomes. There is also evidence of 'harking' – the practice of hypothesizing findings post data-analysis (Munafò et al., 2017). Furthermore, when hypothesized effects are not observed, and null outcomes are reported, publication is

significantly less likely. Moreover, even amongst published findings, there is evidence of selection bias within systematic reviews (Walfisch et al., 2013). If we are to establish a robust evidence base to support nutritional benefits for the ageing brain then the need to pre-register trials with clearly defined hypotheses, explicit outcome measures (particularly with regards to cognitive function), and most importantly, an a priori statistical analysis plan is crucial. For example, an analysis of cognitive function should include pre-intervention baseline data as a covariate since baseline performance or biological state is the strongest predictor of subsequent response. Such an approach will also permit examination of the interaction of baseline measures with nutritional interventions. For example, breakfast interventions in children have been shown to confer greatest benefit to children whose baseline performance is average or less (Adolphus et al., 2017). Such interactions likely also exist in ageing adults. This also highlights the importance of considering characteristics which could influence cognitive performance, such as socio-economic status, IQ, habitual diet, and physiological/metabolic characteristics such as obesity and which if not, taken into account represent residual confounders (Adolphus et al., 2017). Indeed, guidance has been published on evaluating the integrity and strength of evidence (JPT, H. and S, G., 2008), and many resources exist for encouraging best working and research practices in nutrition and health (e.g. (Alexander et al., 2015; Goldacre, 2017; Ioannidis, 2005; Welch et al., 2011)). It would serve our field well to adhere to these recommendations. Taking these steps is likely to increase confidence in the veracity of the research, irrespective of funding source, for all stakeholders, including academics, industry, journalists, and the public.

Furthermore, with increasing pressure to identify and implement strategies that prevent neurodegenerative disease in the context of an ageing population and the considerable personal and financial cost of these conditions, there is a corresponding pressure placed on those in the scientific community to communicate recommendations based on these investigations to the general public and policy-makers in a way that is convincing and accessible. However, within the European Union (EU) there are strict conditions on the use of health claims also in relation to cognition. The legal framework for making health claims within the EU is contained within the Regulation on Food Information for Consumers (FIC) (Regulation (EU) No 1169/2011[4]) and in the Claims Regulation (Regulation (EC) No 1924/2006[5]). These regulations are in place to ensure that information pertaining to food or nutrients are not misleading or attribute them affects which are not supported by sufficient evidence. In addition to ensuring information pertaining to food is clear and understandable; the FIC prohibits medical claims to be made relating to food products, which includes claims targeting the prevention or treatment of a particular disease in humans. In a similar vein, the Claims Regulation defines a health claim as a voluntary message in any form that states or suggests that a food has particular characteristics. In fact, claims should be linked to particular nutrients contained in food products, regarding which it has been shown they have a beneficial effect to human health. These claims include general health claims, health claims targeting children, and disease-risk reduction claims. Cognitive health claims, just like any type of health claim, can only be made regarding a particular food product provided that it has been shown to have a beneficial nutritional or physiological effect, the active nutrient is present in the end product which will produce the claimed effect, and it is present in a form that is bioavailable to the human body. Active ingredients for which so far health claims in relation to cognitive function have been authorized are zinc, copper and iodine. An example of such authorized claim is "*zinc contributes to a regular problem-solving ability*". The Claims Regulation does not apply to purely scientific (i.e. non-commercial) communications, such that evidence-based results regarding specific bioactive nutrients or foods can be communicated provided that there is no direct link to commercial interests. This is different however when communications are targeted at health care professionals, that might end up with the consumer as well. The European Court of Justice has clarified in a 2016 decision[6] that in such context, the Claims Regulation applies as well.

Finally, there remains the obstacle of moving from evidence to implementation of these findings in clinical and public health settings. In the absence of current pharmacological interventions to delay or stop the progression of neurodegenerative disease, a combination of drug and lifestyle interventions appear to be a promising avenue of curtailing the disease processes underlying age-related cognitive decline (Kivipelto et al., 2013; Lombardo, 2012; Martinez-Lapiscina et al., 2013; Morris et al., 2015b; Ngandu et al., 2015; Psaltopoulou et al., 2013; Scarmeas et al., 2006; Valls-Pedret et al., 2015). However, particularly in the context of care homes and services provided specifically to older adults, the adoption of such lifestyle interventions could be costly and would require not only a sound evidence base of the efficacy of certain nutritional and dietary changes, but also practical examples of how these changes can be implemented in a way that is both economical and of optimal benefit to service users in order to ensure these practice are adopted. Indeed, there are such practices emerging in the USA such as the Memory Preservation Nutrition (MPN) program developed by medical practitioners and researchers at Boston University School of Medicine and Tufts University School of Medicine (Emerson Lombardo et al., 2006; Wolf et al., 2012). The MPN implements six key principles including 1) increasing the amount and variety of anti-oxidative nutrients such as vitamin E, vitamin C and β-carotenes (Morris et al., 2002), 2) reducing insulin resistance, 3) reducing LDL cholesterol and avoid trans fats and reduce sugar intake, 4) increasing omega-3 fatty acids and other healthy fats (Okereke et al., 2012) 5) reducing inflammation, and 6) assuring adequate B, C, D, and E vitamins (Kivipelto et al., 2008; Morris et al., 2004, 2005). The MPN program is also updated in line with emerging evidence (Jacka et al., 2017; Parletta et al., 2019) and an additional 7th principle focusing on increasing prebiotic and probiotic intake has been included since 2017. In general, increasing intake of fermented foods including pickled vegetables, leafy greens (e.g. sauerkraut, kimchi), fermented dairy as the preferred form of dairy, and various foods basic to some ethnic diets such as miso, soy or tempeh are recommended. With the aid of dietitians, nutritionists, and educators this program has begun to be implemented in a number of senior residences and programs targeting older adults, as well as individuals across the lifespan. As lifestyle and dietary changes can be challenging to implement, the MPN provides guidelines for adoption of this program by individuals and care providers by including detailed guides, recipes, shopping lists, progress monitoring and coaching (for example see[7],[8],[9]). These practices have begun to be adopted by service providers in the USA. Although the long-term benefits of such practices remain to be determined, programs such as MPN are an example of possible implementation of life-style changes, demonstrating that putting them into practice has the potential to be practical and feasibly adopted by both service providers and recipients.

5. Conclusions

Lifestyle approaches to combatting the growing burden of age-

[4] Regulation (EU) no 1169/2011 of the European Parliament and of the Council of 25 October 2011on the provision of food information to consumers.

[5] Regulation (EC) No 1924/2006 of the European Parliament and of the Council of 20 December 2006 on nutrition and health claims made on foods.

[6] Judgment of the Court (Third Chamber). 14 July 2016.

[7] Emerson Lombardo NB (Nov 2014) Brain Healthy Foods for the Holidays. Acton, MA: Brain Health and Wellness Center®

[8] Emerson Lombardo NB. (Nov 2015) Brain Healthy Foods: Menus and Recipes Vol. 1. Acton, MA: Brain Health and Wellness Center®.

[9] http://brainwellness.com/

related neurodegeneration is receiving increased attention, and the evidence for the impact of diet on disease processes that contribute to pathological brain ageing shows particular promise. Although certain nutrients such as omega-3 fatty acids, flavonoids and B vitamins have been found to impact disease mechanisms underlying cognitive ageing, in light of findings from large-scale observational studies suggesting a complex interplay between nutrients and their impact on health, the focus on the beneficial health effects of specific nutrients has shifted towards multi-nutrient and whole diet approaches to improving brain health.

New avenues for exploring the role of diet in healthy ageing have emerged in recent years, and particularly the impact of the gut microbiome and its manipulation by certain dietary factors, including probiotics and postbiotics, is accumulating promising evidence for the promotion of healthy host brain ageing and general longevity. However, there remain unanswered questions regarding how the impact of the gut microbiome is regulated by diet and its mechanisms of action.

The emergence of new techniques such as imaging measures of brain metabolism, metabolomics and improved measurement of ageing and dietary biomarkers, and novel brain modelling techniques are enabling researchers to approach finding answers to these questions. Improvements in the way we are able to measure the direct relationship between whole food nutrient composition and its impact on health and how this impact changes across different populations and age groups will aid in determining optimal approaches to improving brain health with diet across the lifespan, particularly cognitive ageing as measured by improved neuropsychological tests and their analysis.

Implementation of large-scale preventive interventions based on dietary patterns identified as being beneficial to brain health should be a research and public health priority, ideally in conjunction with other health-promoting lifestyle factors.

There is an increasing societal interest in how lifestyle factors can be modified to prevent cognitive decline and generally improve health over the lifespan. However, there exists an overwhelming amount of inaccurate and conflicting information available from media including the internet, which can often drown out evidence-based recommendations for improving and maintaining health. In light of this, a more robust, accessible, and convincing repository of information regarding how to improve health needs to be made available to the public, while still complying with guidelines and laws pertaining to health claims.

The ultimate aim of this research is to translate these findings into clinical and public health contexts, and indeed early evidence-based programs being currently implemented in aged care settings have shown particular promise. However, further investigation to improve our understanding of the mechanisms by which nutrition can improve brain health across the human lifespan is still required.

CRediT authorship contribution statement

Emma Flanagan: Conceptualization, Writing - original draft, Writing - review & editing. **Daniel Lamport:** Conceptualization, Writing - original draft, Writing - review & editing. **Lorraine Brennan:** Writing - review & editing. **Philip Burnet:** Writing - review & editing. **Vittorio Calabrese:** Conceptualization, Writing - review & editing. **Stephen C. Cunnane:** Writing - review & editing. **Martijn C. de Wilde:** Conceptualization, Writing - review & editing. **Louise Dye:** Conceptualization, Writing - review & editing. **Jonathan A. Farrimond:** Conceptualization. **Nancy Emerson Lombardo:** Writing - review & editing. **Tobias Hartmann:** Writing - review & editing. **Thomas Hartung:** Writing - review & editing. **Marko Kalliomäki:** Writing - review & editing. **Gunther G. Kuhnle:** Writing - review & editing. **Giorgio La Fata:** Conceptualization, Writing - review & editing. **Aleix Sala-Vila:** Writing - review & editing. **Cécilia Samieri:** Writing - review & editing. **A. David Smith:** Writing - review & editing. **Jeremy P.E. Spencer:** Conceptualization, Writing - review & editing. **Sandrine Thuret:** Conceptualization, Writing - review & editing. **Kieran Tuohy:** Writing - review & editing. **Silvia Turroni:** Writing - review & editing. **Wim Vanden Berghe:** Conceptualization, Writing - review & editing. **Martin Verkuijl:** Conceptualization, Writing - review & editing. **Karin Verzijden:** Writing - review & editing. **Mary Yannakoulia:** Writing - review & editing. **Lucie Geurts:** Conceptualization, Writing - review & editing, Supervision, Project administration. **David Vauzour:** Conceptualization, Writing - original draft, Writing - review & editing, Supervision.

Declaration of Competing Interest

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