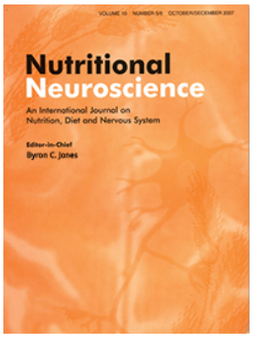

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REVIEW

Effect of nutrition on neurodegenerative diseases. A systematic review

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ABSTRACT

Neurodegenerative diseases are characterized by the progressive functional loss of neurons in the brain, causing cognitive impairment and motoneuron disability. Although multifactorial interactions are evident, nutrition plays an essential role in the pathogenesis and evolution of these diseases. A systematic literature search was performed, and the prevalence of studies evaluated the effect of the Mediterranean diet (MeDiet), nutritional support, EPA and DHA, and vitamins on memory and cognition impairment. The data showed that malnutrition and low body mass index (BMI) is correlated with the higher development of dementia and mortality. MeDiet, nutritional support, and calorie-controlled diets play a protective effect against cognitive decline, Alzheimer's disease (AD), Parkinson disease (PD) while malnutrition and insulin resistance represent significant risk factors. Malnutrition activates also the gut-microbiota-brain axis dysfunction that exacerbate neurogenerative process. Omega-3 and -6, and the vitamins supplementation seem to be less effective in protecting neuron degeneration. Insulin activity is a prevalent factor contributing to brain health while malnutrition correlated with the higher development of dementia and mortality.

KEYWORDS

Nutrition; diet; Alzheimer' disease; Parkinson' disease; Huntington disease; multiple sclerosis; amyotrophic lateral sclerosis; cognitive impairment

Introduction

Neurodegenerative diseases are characterized by the loss of the brain neurons activity, causing progressive impairment of cognitive function. Neurodegenerative disorders and dementia are increasing progressively with an incidence of 17.2 million people worldwide. A 10–25% reduction in risk factors could potentially prevent as many as 1.1–3.0 million AD cases worldwide and 184,000–492,000 cases in the USA [1]. The role of epigenetic factors in the development of neurodegenerative disease has been largely investigated evidencing the relevance of DNA and histone modifications and non-coding RNA in the etiology of these disorders [2].

Alzheimer's disease (AD) is the most frequent cause of dementia that contributes for 70% to the world global incidence of dementia is as high as 24 million and has been predicted to quadruple by the year 2050 [3]. The neuropathological characteristics of the AD show diffuse extracellular amyloid plaques in the brain that are frequently surrounded by dystrophic neurites and intraneuronal neurofibrillary tangles [3]. The etiology of the AD is not entirely understood, but likely seems to be the result of both genetic and environmental factors. Aging is a determinant factor because the incidence of the AD at 80 years is four-fold greater than at 70 and nine-fold than 65 years [4]. Cardiometabolic risk factors such as obesity, diabetes, hypertension, cardiovascular diseases, smoking, low physical activity are involved in the dementia process [4]. In Europe, data between 1994 and 2013 from the Eurostat and World Health Organization database showed an increase for AD deaths, especially in eastern and northern European countries such as Slovakia, Lithuania, and Romania and in the female population [5]. The prevalence of AD is significantly lower in Asian populations compared with western Europe, North America and Australia and a prevalent genetic and prion disorder were found [6], suggesting that nutrition can be involved in the neurodegenerative process [7]. In patients with AD, an alteration in eating behavior of about 50%-60 [8] and a poor nutritional condition of 18%-80% [9] was observed. Weight loss is a consequence and seems to be associated with cortical amyloid burden evident at the pre-clinical stage [10]. Although the aging process has a determinant role in the development of AD [11], genes, chronic inflammation, mitochondrial, metabolic dysfunctions, impaired insulin signaling, oxidative stress, as well as metal ion dyshomeostasis synergistically work to

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promote AD. Sex differences in the incidence of neurodegenerative diseases are related to the sex hormones effect on oxidative stress [12].

Parkinson's disease (PD) is characterized by neuronal degeneration due to a dopaminergic loss in the substantia nigra. The preliminary dysfunction in PD appears as motor neuron alteration, tremors, loss of muscular strength, and subsequent cognitive decline and dementia [13]. The dysfunction in PD may result from a reduction in dopaminergic, cholinergic, and other non-dopaminergic neurotransmitters, and structural deficiency, including hippocampal and cortical atrophy, especially of the posterior occipital cortices [14]. Dementia in PD is particularly prevalent in advanced age, resulting in high morbidity and mortality in approximately 80–90% of cases. The pathogenetic mechanisms of PD are not clearly explained, but recently, the insulin resistance has been evidenced [15,16] suggesting a correlation between the alteration of glucose metabolism with neurodegeneration.

Amyotrophic lateral sclerosis (ALS) [17], is characterized by the motor neuron degeneration of the corticospinal tract, brainstem, motoneuron of the spinal cord, with consequent progressive muscle atrophy and paralysis, and respiratory failure. Median survival is of 2-4 years [18]. ALS has an incidence of approximately 3.9–8 per 100,000 individuals in the United States (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5370581/#R1) and an increase of 69% is expected mainly in the developing nations [19]. ALS is a severe disease because the medium survival changes from 20 to 48 months, and only 10–20% of patients survive longer than ten years. ALS is a multifactorial interacting agent, but a genetic origin is present in approximately 30% of familial ALS cases [20]. Genetic and environmental factors may interact in the genesis of ALS [21], but also viruses are receiving strong evidence [22]. Motor neurons in ALS present metabolic alteration at the mitochondria level with a change in lipid oxidation, leading to increased glycolysis, showing that metabolic intervention can represent a therapeutic strategy [23]. Great interest is growing about the role of nutrition in the pathogenesis and development of ALS [24,25]. O'Reilly et al. [26] found that a lower premorbid BMI was associated with an increased risk of developing ALS compared to overweight and obese and a higher BMI correlated with more prolonged survival [27]. However, weight loss in ALS patients is evident also when they had regular nutrition [28]. In ALS the most suspected risk factors are sports activity, chemical, smoking and diet [29]. ALS and frontotemporal dementia are different diseases with a similar clinical and pathological condition [30].

Multiple sclerosis (MS) is a disease of the central nervous system (CNS) activated by an immune-mediated inflammation process which causes demyelination and subsequent axonal damage with invaliding evolution due to the loss of motor and sensory function [31]. MS shows a broad clinical aspects varying from loss of vision, neuromuscular disorder, paraplegia, spasticity that can appear in various part of the body and is more frequent in young adults. There are two prevalent forms of clinical aspects: the relapsing-remitting MS (RRMS) in 85% of cases and the primary progressive MS (PPMS) [32]. The prevalence of MS has a geographic distribution with the highest incidence in developed countries, particularly in the Orkney Islands, Scotland (250 per 100 000), in Norway (208 per 100 000) wherein the last 8-9 decades has increased of 10-fold [33]; followed by Hungary, Slovenia, Germany, USA, Canada and Czech Republic (130 per 100 000). MS is rare in Japan (2 per 100 000) and is almost unknown in India [34]. Several animal and human studies have shown that CD4+ T helper 17 (Th17) cells and their downstream pathways are implicated in the pathogenesis of MS and neuromyelitis optica [35]. Many environmental factors are involved in modulating the activity of Th17 pathways, so as the alteration in the diet (Western diet), low vitamin D, exposure to infections, and other factors can potentially change the risk of development of autoimmunity. The pathogenesis of Ms a complex multifactorial interaction not yet elucidated, but genetic and epigenetic factors in the pathogenesis of this disorder are involved. However, genetic susceptibility cannot explain this autoimmune disease alone [36].

The geographical distribution and the effect of migration on MS incidence (patients migrated from a Country with high frequency to another with low impact before the age of 15 years had a reduced risk of MS) support the nutritional role as a risk factor more than infections or environmental factors [37]. However, systematic reviews found that dietary intervention had no apparent beneficial effect in patients with MS [38,39]. Other risk factors, such as vitamin D and smoking, might have involved in the development of MS incidence and further investigations are needed to increase survival in MS.[33]

Huntington's disease (HD) is s a progressive brain disorder caused by the expansion of a CAG (trinucleotide cytosine-adenine-guanine) repeat in the huntingtin gene. This mutation results in the production of the polyglutamine-expanded huntingtin protein (mHtt), leading to involuntary choreiform movements, cognitive impairment, and neuropsychiatric symptoms one of the most devastating genetic neurodegenerative disorders with no valid medical therapy [40]. The exact

mechanism of the disease progression has not been elucidated. mHtt causes transcriptional dysregulation, which can lead to neuronal cell death in the brain [41]. Many defects in mitochondria have been observed in various HD mouse models [42], cell models, and patients, and the striatum is the brain region that is particularly vulnerable to mitochondrial impairment [43]. Alteration of energy metabolism may be involved in the pathogenesis of HD. It was shown that HD patients with a higher BMI have a slower progression of the disease [44].

The common histopathologic feature of the AD, PD, and HC is characterized by the loss of neurons and the accumulation of disease-specific aberrant proteins. As prevalent pathogenetic factor has been proposed oxidative stress, mitochondrial dysfunction, and impaired autophagy systems to cleave modified denatured proteins [45,46]. The oxidative stress has been considered as the primary role in the pathogenesis of AD, PD, and HD and metabolic and mitochondrial improvement can be protective against these diseases [47]. Interestingly, a recent meta-analysis by Liang et al. [48] showed that natural therapy, such as physical exercise or cognitive training, might have a better effect than pharmacologic therapies in the treatment of AD. This study aims to evaluate the impact of nutrition on the development of neurodegenerative diseases.

Methods

In this systematic review, the PRISMA guidelines have been followed [49]. The literature search was performed using Medline, EMBASE, and the Cochrane Central Register of Controlled Trials. Additional studies were identified through a crossroad of the bibliography. A combination of the following keywords was used: 'nutrition' and 'diet' with 'neurodegenerative diseases,' 'Alzheimer's disease,' 'amyotrophic lateral sclerosis,' and 'Parkinson's disease,' 'Huntington disease,' and 'multiple sclerosis.' Search term included a randomized controlled clinical trial, and double-blind method. In this systematic review have been included studies published from 2000 until now. The inclusion criteria were: studies which described the diet intervention, the adherence to the dietary pattern, the evaluation of food intake, and the method of assessment of cognitive impairment. Studies including exercise activity, medical and nutraceutical formulations supplementation were excluded. Uncompleted studies that did not evaluate the mental impairment, or without a control group have also been banned. The research method is represented in the flowchart (Figure 1).

Results

We retrieved 546 articles, 79 have been selected after removal of duplicate and of the items that did not reach the criteria of low risk of bias. The studies were divided into four groups: twenty-eight on the effect of nutrition, eighteen of supplements, sixteen of polyunsaturated fat and thirteen of vitamins on neurodegenerative disease, Large differences between the duration of the studies, (varying from 3 weeks [50] until 14 years [51]) and the number of patients involved in the study, from 24 [52] until 185.000 [53], has been observed. The age of patients varied widely from 49.4 [53] until 86.9 years [54]. We found twenty-eight studies investigated the correlation between nutrition and neurodegenerative diseases [53,55–81], which are reported in Table 1. Prevalence of the studies investigated the effect of the Mediterranean diet (MeDiet) on cognitive impairment and the progression of AD while other evaluated the effect of antioxidant nutrients of the food on ALS [56], and in HD [66]. The majority of these studies found a beneficial effect of MeDiet improving cognitive impairment in the general population and in AD incidence, and a reduced mortality rate. Collectively, ten cohort studies, including 37,263 participants [57,60,63,69,70,74–77,79], three double-blind, randomized clinical trials [62,67,78], and some observational studies [55,64,80] showed that a high adherence to the MeDiet had a protective effect on the cognitive decline and AD progression over time.

Interestingly, some researchers evaluated the effect of nutrition on brain structures volume and function. Gu et al. [75] in a community-based study of 674 elderly with a mean age of 80.1 years, evaluated the brain volume, total gray and white matter volume and the cortical thickness by high-resolution magnetic resonance imaging (MRI). They found a correlation between low adherence to MeDiet and reduced volume of the brain structures investigated. Likewise, Mosconi et al. [64] in 54 healthy subjects, examined the brain regions of AD and cognitive control by MRI, showed that low adherence to MeDiet correlated with the atrophy of these zones. Bertiet al. [55] found that low adherence to MeDiet was associated with amyloid-β and neurodegeneration estimated by positron emission tomography (PET) and MRI.

Only a few studies did not find any positive impact of MeDiet on the cognitive decline [68,71–73]. Rotstain et al. [53] did not observe in a large population of women, slightly association between the diet quality and the risk of developing MS. Vercambre et al. [73] and Samieri et al. [71] investigated healthy professional women, highly educated, who underwent a telephone cognitive battery tests of global cognition, verbal memory, and nutritional habit with food frequency

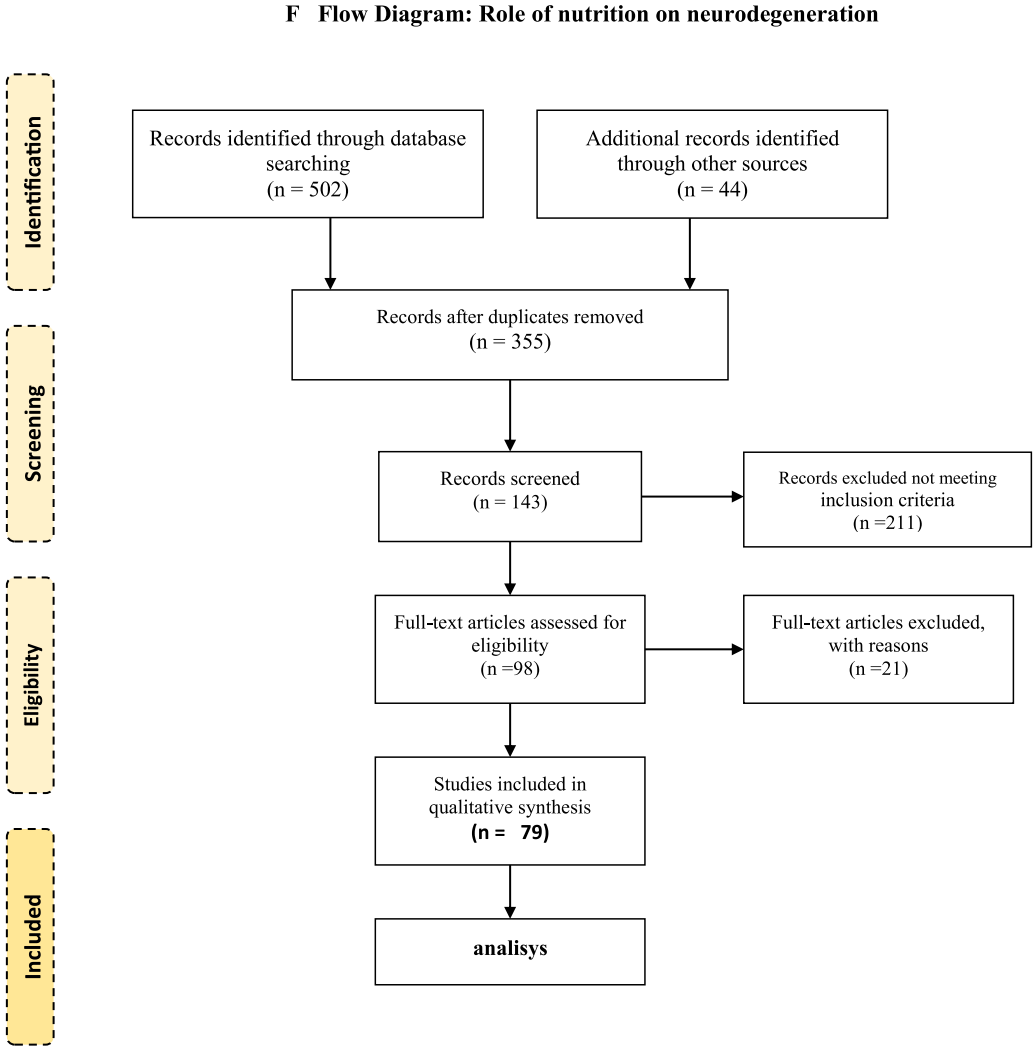

Figure 1. Flow chart showing the methodology of selection of the articles.

questionnaire. They did not find any positive effect of MeDiet on cognitive function. However, the professional and education level does not represent the usual standard in a healthy population, and telephone investigation represents a significant limiting factor. Kesse-Guyot et al. [68] observed the association of MeDiet and cognitive performance in a large community of 3083 subjects for 13 years, and they did not find a beneficial effect of MeDiet. Cherbuin et al. [72] conducted an extensive longitudinal investigation 1528 healthy people, with a medium age of 62.5 years, and no protection of MeDiet on cognitive function was found. These data underline that the accuracy of the methodology of investigation is critical to obtain significant and coherent results.

Eighteen studies evaluated the effect of nutritional support on neurodegenerative diseases [50,82–98] and are summarized in Table 2. It was shown that dietary supplementation and education on food intake had a positive impact on quality of life and cognitive function in patients with AD [50,84,85,87,88,96–98], an improvement in movement disorders in PD [82,88], and a reduction in disability scale in MS [83], also in ALS [56]. Conversely, several studies did not find any positive effect on reducing cognitive decline in patients with AD and HD [86,91,94,98,99]. Despite a nutritional supplementation improved body composition and reduce morbidity and mortality [96] had no positive influence on cognition [93,95]. However, the type of nutritional support changed significantly. Most studies supplemented the dietary habit of patients increasing food intake. Others, supplemented with protein (30 gr/day) [85], active drink [98], probiotic milk (200 ml/day) [84], nutraceutical formulation (folate, tocopherol, Vit. B12, adenosyl methioinine, N-acetyl cysteine, acetyl-L-carnitine) [52], and probiotics (selenium 200 mg plus Lactobacillus acidophilus, Bifidobacterium bifidum, and Bifidobacterium longum) [82]. A higher protein intake improved time reaction, but not cognitive performance [85].

However, in some studies that showed clinical improvement after nutritional supplementation, the

risk of bias exists. For example, Tamtaj et al. [100] who found clinical benefit in patients with PD after three months of supplementation, the most evident variation in blood parameters was glucose and insulin improvement while no data about calorie ingestion and changes in body weight were given. So, it is possible to argue that the clinical outcome could be related more to the nutritional changes rather than supplements.

Polyunsaturated fatty acids (PuFa)

Among the retrieved article, seventeen investigated the effect of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) on cognitive function presented more controversial results [54,101–115] and summarized in Table 3. All studies were randomized, double-blind, placebo-controlled trials, and the duration varied from three months until five years. Most studies showed no beneficial effect of eicosapentaenoic (EPA) and docosahexaenoic acid (DHA) administration on dementia and cognitive decline also over three years in elderly people with memory complaints [101]. Some studies found a significant improvement in cognition and memory in healthy [105,111] and AD patients after supplementation with EPA and DHA [103,106].

Jerneren et al. [116] showed that the beneficial effect of omega-3 fatty acids on brain atrophy might be confined to subjects with physiological B vitamin status, underlining the importance of identifying subgroups likely to benefit in clinical outcomes [105,116] to reduce the amount of the amyloid-β-induced toxicity [117]. However, Yip et al. [118] found that EPA administration at high doses (300 mg/kg/day) showed a significant increase in a highly toxic product (4-hydroxy-2-hexenal) derived from the oxidation of omega-3 fatty acids causing a detrimental effect in ALS patients [119].

Vitamins

Thirteen studies investigated the effect of vitamins supplementation on cognitive performance and dementia [51,86,116,119–128] and summarized in Table 4. Most of the studies showed no effect of vitamins and mineral supplementation on cognitive function and AD progression. A few found that a high-dose of B vitamin supplementation was beneficial in patients with cognitive dysfunction [52,116,123,126,128]. Ascherio et al. [128] in a large population study found that vitamin E supplementation lowered the risk of ALS, but not among the user of other vitamins. A recent meta-analysis confirmed that vitamin E seems to have also some beneficial effect in preventing AD [129]. However, other studies did not find any positive impact mediated by vitamins supplementation on cognitive function [51,119,122,124,125]. A double-blind, randomized clinical trial conducted for six years on a population of 7540 men, at least 60 years old, found that the supplementation with vitamin E, selenium, had no beneficial effect on an AD prevention [122]. However, vitamin E may be detrimental when not effective in preventing oxidative stress [130]. Although in patients with AD, a low plasma level of vitamin C was found [131], but the beneficial effect of vitamin C administration in the prevention and treatment of AD is still lacking [51]. Folic acid in patients with AD caused a reduction of inflammatory markers (IL-6, TNF-α) and a slight cognitive improvement [123]. Vitamin B_6 and B_{12} supplementation did not show any effect on slowing cognitive decline in individuals with mild to moderate AD [119,127] while found a positive impact of vitamins administration (vitamin C, vitamin E) [52] on cognitive maintenance. Chandra et al. [132] found significant cognitive improvement after one year of vitamins and trace elements, but the study received various arguments about the application of the mental test. The efficacy of vitamins supplementation remains to be demonstrated, though they can have some positive influence on the progression of cognitive impairment and AD, their impact seems related to other metabolic condition.

Carlson et al. [133] showed that Ginkgo-biloba administration in seventy-eight subjects for four months had no positive effect on cognitive impairment.

Limiting factors in the studies

In epidemiologic studies, the dietary assessment by the FFQ (food frequency Questionnaire) can represent a source of bias depending on the modality to collect the data, mediated by the interviewer or self-administered and via a phone call evidencing some discrepancies [134]. The duration of observation is utmost important.

Discussion

Effect of nutrition on neurodegeneration

The overall number of studies showed that high adherence to MeDiet is associated with a reduced risk of developing mild cognitive impairment and AD. The characteristic of MeDiet is expressed by the abundance of fruit and vegetables, unrefined carbohydrates as bread and pasta, cereals and potatoes, fish, olive oil, red wine, and reduced fat intake. The beneficial effects of MeDiet against the risk of the AD and cognitive decline are related to the quality and the quantity of

Table 1. Effect of nutrition on neurodegenerative diseases.

Authors	N. pat.	Age	Study	Diet	Duration (years)	Comments
Rosestain, 2018 [53]	185,000 women Nurses health Study	49.4	Follow-up	AHEI-2010 aMED DASH (FFQ)	4	None of the dietary indices was correlated with the risk of developing MS among women.
Berti, 2018 [55]	70 cognitive normal	30-60	Follow-up	MeDiet	3	Lower MeDiet adherence was associated with progressive AD abnormalities evaluated with brain imaging study.
Nieves, 2016 [56]	302 ALS	63.2	Cross sectional study	Nutrient intake, measured by the Block Food Frequency Questionnaire (Kcal 1740)	5	Higher intake of antioxidants, carotenes, fruits, and vegetables correlated with higher ALS function.
Anastasiou, 2017 [57]	1865 (41%M) dementia	73	Longitudinal studies	MeDiet Kcal 1782 CHO = 39% *P* = 14% L = 47%	1.4	MeDiet Score was associated with a 10% decrease in dementia. Fish negatively and cereal positive correlated with mental performance.
Knight, 2016 [58]	137 healthy	72.1	randomised controlled trial	MeDiet compared to habitual diet	1.5	No evidence of a beneficial effect of a MeDiet on cognitive function.
Gu, 2015 [75]	674 without dementia	80.1	cross-sectional study	MeDiet adherence	___	Total brain volume (TBV), total gray matter volume (TGMV), total white matter volume (TWMV), mean cortical thickness evaluated with RMI showed that MeDi adherence was associated with less brain atrophy,
Olsson, 2015 [59]	1138 M cognitive normal	71	Longitudinal Studies	FFQ 7 days	12	No strong associations with development of cognitive dysfunction for any of the dietary patterns investigated.
Qin, 2015 [60]	1650 community dwellers	63.6	Prospective Studies	24-hour recalls over 3 days.	5.3	MeDiet reduce the rate of cognitive decline.
Trichopoulou, 2015 [61]	401 healthy	74	Prospective Studies	MeDiet adherence (FFQ)	6.6	MeDiet highly protected against cognitive decline.
Valls-Pedret, 2015 [62]	447 cognitive normal	68.2	Randomized Controlled Trial	MeDiet+ extra virgin olive oil + nuts (30gr/day) Control	4.1	MeDiet supplemented with olive oil or nuts was associated with improved cognitive function.
Zbeida, 2014 [63]	4577 NHANES	71.1	Prospective Studies	MeDiet adherence (FFQ)	1	MeDiet was associated with better physical efficiency, attenuated on cognitive function.
Mosconi, 2014 [64]	52 cognitive normal	54	Cross-Sectional Studies	MeDiet adherence (FFQ)	____	Lower adherence to the MedDiet had cortical thinning in the same brain regions as clinical AD patients with MRI measures.
Ozawa, 2013 [65]	1006 cognitive normal	60-79	Prospective Studies	SFFQ	15	Reduced risk of dementia associated with the higher intake of soybean, vegetables, milk, and lower intake of rice.
Marder, 2013 [66]	211 subjects with an expanded CAG repeat.	44.1	Prospective Studies	MeDiet kcal 1847-1785	3.4	Diet and high energy intake in premanifest HD may delay the onset of HD.
Martinez-Lapiscina, 2013 [67]	522 High vascular risk	74.6	Double-blind Randomised trials	MeDiet supplemented with olive oil	6.5	MeDiet improved cognition compared with a low-fat diet.
Kesse-Guyot, 2013 [68]	3083 healthy (1655 M)	52	Randomized Controlled Trial	Med Diet adherence (FFQ)	13	No beneficial effect of MeDiet adherence on cognitive function, irrespective of educational level, which is the strongest indicator of cognitive reserve.
Ye, 2013 [69]	1269 cognitive normal	57.3	Prospective Studies	MeDiet adherence (FFQ)	1	MeDiet was associated with higher mental performance.
Wengreen, 2013 [79]	3831 (M and W)	74	Prospective Studies	MeDiet nutrient component rank scores were summed	10.6	MeDiet was associated with consistently higher levels of cognitive function in elderly men and women.
Tsivgoulis, 2013 [70]	17.478 cognitive normal	64.4	Prospective Studies	SFFQ	4	Higher adherence to MeDiet was associated with a lower cognitive impairment.
Samieri, 2013 [71]	6147 W cognitive normal	72	Follow-Up Studies	MeDiet adherence (FFQ)	5	No association between MeDiet with cognitive decline.
Cherbuin, 2012 [72]	1528 cognitive normal	62.5	Prospective Studies	MeDiet (FFQ)	4	Adherence to MeDiet was not protective against cognitive decline but excessive caloric intake, and fat intake.
Gardener, 2012 [80]	149 AD 98 MCI 723 HD	77.5 76 69.9	Cross Sectional Studies	MeDiet Kcal 1702 Kcal 1710 Kcal 1691	1.5	AD and MCI participants had a lower adherence to the MeDiet than HD participants.
Vercambre, 2012 [73]	2505 WACS	72.5 75.4	Prospective Studies	MeDiet adherence	5.4 7.6	No cognitive change in women with high CVD risk was associated with MedDiet adherence.

(*Continued*)

Table 1. Continued.

Authors	N. pat.	Age	Study	Diet	Duration (years)	Comments
Tangney, 2011 [74]	3790 (2280 blaks) (1510 whites)		Prospective Studies	DASH and MeDiet score adherence		The MeDiet pattern may reduce the rate of cognitive decline with older age.
Gu, 2010 [81]	1219 non-demented (66% W)	76.7	Cross-Sectional Studies	MeDiet SFFQ	4	Adherence to MeDiet and lower risk of AD did not seem to be mediated by hsCRP, fasting insulin, or adiponectin.
Feart, 2009 [76]	1410 not demented	75.9	Prospective studies	MeDiet adherence (FFQ)	5	Higher adherence to MeDiet was associated with slower cognitive decline evaluated with MMSE, but not consistently with other cognitive tests.
Scarmeas, 2009 [77]	1393 Normal 482 MCI	76.7 77.5	Cohort Studies	MeDiet Kcal 1425	4,5	High adherence to MeDiet was associated with a reduced risk of mild cognitive impairment and AD.
Scarmeas, 2007 [78]	192 AD	82.9	Prospective studies	MeDiet Kcal 1466	1.5	Higher adherence to the MeDiet is associated with lower mortality in AD.

M = men; W = women; AD = Alzheimer's disease; PD = Parkinson's disease; Souvenaid = multinutrient drink; CR*P* = C reactive protein; SFFQ = semiquantitative food frequency questionnaires; FFQ = food frequency questionnaire; AHEI-2010 = Alternative Healthy Eating Index-2010; aMED = Alternate Mediterranean Diet (aMED) index; DASH = Dietary Approaches to Stop Hypertension; MMSE = Mini-Mental State Examination; WACS = Women's Antioxidant Cardiovascular Study

food with a consequent reduction in insulin resistance and AD risk [135]. The best results emerged in trials with controlled calorie intake [57,62,70,77,78,136]. The best clinical improvement was found in patients who followed a MeDiet regimen with low energy, low CHO, and high fat intake, as shown by Anastasiou et al. [57] with a diet of Kcal 1782, CHO intake of 39%, proteins of 14%, and fat of 47%. In Scarmeas et al. studies [77,78] the diets had Kcal 1425 and 1466 respectively, and in others [66,80] the caloric intake was about Kcal 1700 and 1800. The MedDiet in these studies also meets the criteria of macronutrient composition and energy requirement that can change the metabolic condition at the brain level with low CHO and high fat intake that can explain the cognitive benefits through the reduction of insulin level, not observed in another study.

In Dementia-free Framingham Heart Study, participants had been measured for pro-inflammatory biomarkers and were followed up prospectively for the development of AD and all-cause dementia. Over a mean follow-up period of 13 years, 159 persons developed dementia (including 125 with AD). After adjustment for other risk factors, only adiponectin in women was associated with an increased risk of all-cause dementia [137]. Considering that various studies had a low-quality score, it remains uncertain if the effect of MeDiet were more related to the type of nutrients or the reduction of calorie intake. A recent meta-analysis demonstrated that the MeDiet score had a linear relationship with the incidence of cognitive impairment and the median score level was not correlated with any benefit [138] while another did not reach specific date about the effect of MeDiet on neurodegenerative diseases [139]. However, MeDiet studies may have some bias due to the different score used for MeDit calculation and the application of the FFQ (food frequency questionnaire). In particular, the FFQ is an interview method which can include bias depending on the modality if self-administered or conducted by a trained interviewer [134]. Better results are guaranteed when performed by a trained interviewer and via face to face than via a phone call. In patients with low adherence to MeDiet, it was documented by MRI brain image a progressive increase of AD biomarkers [55] and a cortical thinning similar to that observed in AD patients [64].

Further prospective-cohort studies with longer follow-up and randomized controlled trials are warranted [139].

Nutritional support in neurodegenerative diseases

Undernutrition and losing weight in patients with cognitive impairment are the most harmful effect on brain function and mortality, worsening the neurodegenerative process. Hanson [140] showed that weight loss is a predictor of death in advanced dementia The most common date emerged is that malnutrition and low BMI correlated with the higher development of dementia and mortality, showing that nutrition is involved in the neurodegenerative process [7]. Ticinesi et al. [141] found that enteral nutrition in patients with dementia increased the risk of mortality compared to oral feeding (70% vs. 40%) and should be discouraged, probably because it does not support the minimum nutritional need. In underweight patients affected by PD, malnutrition is correlated with a more inferior quality of life [88,141]. A decrease in BMI in PD patients is a predictor of cognitive decline [142], of future dementia, and nutritional

Table 2. Effect of nutritional supplements on neurodegenerative diseases.

Authors	Patients	Age	Study	Supplements	Duration	Clinical outcomes
Tamtaij, 2018 [82]	60 PD	68.2	RDBCL	selenium (200 mug/day) plus probiotic (Lactobacillus acidophilus, Bifidobacterium bifidum, and Bifidobacterium longum)	3 months	Significant reduction in insulin and CRP level and improvement in MDS-UPDRS
Soininen, 2017 [98]	311 prodromal AD	71	RDBCL	active product (125 mL once-a-day drink Souvenaid) *	51 months	Multinutrient intervention had no significant effect on neuropsychological test.
Kouchaki, 2017 [83]	60 MS	34.4	RCT	Probiotic (Lactobacillus acidophilus, Lactobacillus casei, Bifidobacterium bifidum and Lactobacillus fermentum)	12 weeks	Improvement in EDSS and depression; reduction in insulin and CRP level.
Akbari, 2016 [84]	60 AD	77.6	RDBCL	200 ml/day probiotic milk *	12 weeks	significant improvement in the MMSE, no effect on inflammatory markers
Van der Zwaluw, 2014 [85]	65 frail or pre frail	79	RCT	Protein 30 gr/day	24 weeks	Protein supplementation improved reaction time
Remington, 2016 [86]	34 mild cognitive impairment	78.4	RCT	nutraceutical formulation (folate, alpha-tocopherol, B12, S-adenosyl methioinine, N-acetyl cysteine, acetyl-L-carnitine)	6 months	Improvement of cognition with the Dementia Rating Scale
Suominen, 2015 [87]	78 AD	74,7	RCT	< 1.2 g/bodyweight	12 months	Improves nutrition and HRQoL, and may prevent falls among AD people.
Sheard, 2014 [88]	125 PD	70	RCT	Nutrition assessment by FFQ	12 weeks	In malnourished PD dietetic intervention improved quality of life.
Kwok, 2013 [89]	429 Not demented	83	RCT	Dietary support (menu changes or advice)	5 years	Dietary intervention did not reduce significantly cognitive decline.
Jyvakorpi, 2012 [90]	102 AD	>65	RCT	Tailored nutritional care	1 year	Tailored nutritional care is beneficial to home-dwelling AD patients.
Salvà, 2011 [99]	946 AD (293 completed)	68	RCT	Diet training intervention	12 months	NutriAlz program had no effect on functional decline in Alzheimer disease patients.
Pivi, 2011 [91]	90 probable AD	65	RCT	Nutritional supplementation.	6 months	Nutritional supplementation improves cognitive function
Salas-Salvado, 2005 [93]	53 AD	72	RCT	Lyophilized foods and nutritional advice	3 months	Positive impact on nutritional status, body weight increased, no improvement in cognitive function.
Trejo, 2005 [94]	30 Hugtington disease	46	RCT	extra 473 kcal	3 months	No changes in body mass index. Neurologic evaluation did not change significantly.
Young, 2004 [50]	34 probable AD	69	RCT	Nutrition supplements	3 weeks	BMI increased, less aberrant motor problems, less mental disorganization, and increased attention.
Lauque, 2004 [95]	91 AD	≥65	RCT	Nutritional supplements	3 months	A significant increase in weight and fat-free mass, but no changes in cognitive function.
Gil Gregorio, 2003 [96]	99 AD	86.5	RCT	Nutritional supplements	12 months	Nutritional supplements applied to a group of patients with AD living in nursing-homes can reduce morbidity and mortality.
Riviere, 2001 [97]	151 AD	71	RCT	Nutritional intervention	12 months	Nutritional educational program in AD patients could have a positive effect on patients' weight and cognitive function.

MDS-UPDRS=Movement Disorders Society-Unified Parkinson's Disease Rating Scale; EDSS = Expanded disability status scale; MMSE= Mini-mental state examination; RCT=randomized controlled trial; RDBCL=randomized, double-blind, and controlled clinical trial

**Lactobacillus acidophilus, Lactobacillus casei, Bifidobacterium bifidum*, and *Lactobacillus fermentum*

Table 3. Effect of EPA and DHA supplementation on cognitive impairment.

Authors	Patients	Age	Study	Supplementation	Duration	Clinical outcomes
Baleztena, 2018 [54]	99 elderly CI and MCI	86.9	RCT	DHA 250 mg, EPA 40 mg, vitamin E 5 mg, phosphatidylserine 15 mg, tryptophan 95 mg, vitamin B 12 5 µg, folate 250 µg and ginkgo biloba 60 mg	1 year	No improvement in the global cognitive function in elderly people without CI or with MCI.
Andrieu, 2017 [101]	1680 Cognitive normal	70	RCT	800 mg docosahexaenoic acid and 225 mg eicosapentaenoic acid),	3 years	No significant effects of polyunsaturated fatty acids on cognitive decline.
Mazereeuw, 2016 [102]	92 cognitive healthy	61.7	RCT	n-3 PUFA (1.9 gr/day)	3 months	No improvement of depressive and cognitive symptoms.
Zhang, 2016 [103]	240 Mild cognitive impairment	65	RCT	DHA 2 g/day	1 year	Significantly improvement in cognitive function and slow the progression of hippocampal atrophy.
Jackson, 2016 [104]	86 cognitive healthy	50-70	RCT	Fish oil (DHA 896 mg, EPA 128 mg) Ephalex Active 50 + 2 gr DHA-fish oil + phosphatidylserine mg 88 + Ginko Biloba mg 240 + mg 1 folic acid + vitamin B12 mg 24.	6 months	No effect of either active treatment was found for any of the oxygenated hemoglobin [1]Near Infrared Spectroscopy measures or on the cognitive performance.
Kulzow, 2016 [105]	44 cognitive healthy	59.6	RCT	n-3 PUFA 2.2 gr/day	6.5 months	Positive effects on memory functions in healthy older adults.
Eriksdotter, 2016 [106]	174 AD	74	RCT	2.3 g omega-3 FA	6 months	Significative improvement of cognitive impairment with a dose-response relationship.
Chew, 2015 [107]	3073 risk of mavular degenration. Cognitive healthy	72.7	RCT	n-3 PUFA 1 gr and/or lutein (10 mg)/zeaxanthin (2 mg).	5 years	No cognitive improvement
Phillips, 2015 [108]	57 cognitive impairment 19 AD	71.1	RCT	EPA mg. 600 + DHA mg. 625/day	4 months	No significant effect on cognitive impairment and dementia
Jeremka, 2014 [110]	138 cognitive healthy	51	RCT	1.25 gr/day n-3PUFA 2.50 gr/day n-3 PUFA placebo	4 months	Attenuation of loneliness-related verbal episodic memory declines over time.
Witte, 2014 [111]	65 cognitive healthy	63.9	RCT	n-3 PUFA (1320 mg EPA + 880 mg DHA) placebo	6.5 months	Improvement of cognitive performance, structural neuroimaging, vascular markers.
Mahmoudi, 2014 [112]	199 normal or moderate cognition impairment	>65	RCT	180 mg of DHA + 120 mg. of EPA	6 months	No cognitive improvement.
Geleijnse, 2012 [109]	2911 CD, cognitive healthy	60-80	RCT	EPA-DHA, 2 g/d	40 months	No effect of dietary doses of n-3 fatty acids on global cognitive decline.
Yurko-Mauro, 2010 [113]	485 healthy	≥55	RCT	900 mg/d of DHA	6 months	Improved learning and memory function with DHA.
van de Rest, 2008 [114]	302 cognitive helthy	70	RCT	1,800 mg/d EPA-DHA, 400 mg/d EPA-DHA,	6.5 months	No effect of EPA and DHA supplementation on cognitive performance.
Freund-Levi, 2006 [115]	204 AD	74	RCT	DHA 1.7 g/day EPA 0.6 g/day	6 months	No effect on the delay of cognitive decline.

EPA = eicosapentaenoic acid; DHA = docosahexaenoic acid; CI = cognitive impairment; MCI = mild cognitive impairment; CD = coronary disease; RCT = randomized, double-blind, placebo-controlled.

Table 4. Effect of vitamins supplementation on neurodegenerative diseases.

Authors	Patients	Age	Vitamin supplementation	duration	Clinical outcomes
Liu, 2018 [120]	7781 Europen descendent individuals	45	AD genome associated with vit. E	___	No significant association between vitamin E and AD.
Hiller, 2018 [121]	51 PD	66.5	Vitamin D 10,000 IU/day	4 months	No significative improvement in PD patients measured by the Sensory Organization Test.
Kryscio, 2017 [122]	7540 M	67.5	Vitamin E, Vit. E + Selenium, placebo	6 years	No effect of antioxidant and vitamin E supplementation to prevented dementia.
Kwok, 2017 [119]	271 diabetic non demented	70	methylcobalamin 1000 µg	27 months	Vitamin B12 supplementation did not prevent cognitive decline in older diabetic patients.
Remington, 2016 [52]	24 AD	75	Folate, alpha-tocopherol, B12, S-adenosyl methioinine, N-acetyl cysteine, acetyl-L-carnitine	1 year	Improvement in cognitive performance.
Chen, 2016 [123]	121 AD	≥60	Folic acid (1.25 mg/d)	6 months	Folic acid is beneficial in patients with AD with a slight improvement in mental test.
Dangour, 2015 [124]	201 older with low vit. B12	80	Vitamin B12 mg 1	11 year	No effects on peripheral nerve and cognitive function.
Jerneren, 2015 [116]	168 mild cognitive impairment	70	High-dose B vitamin supplementation (folic acid, 0.8 mg; vitamin B-6, 20 mg; vitamin B-12, 0.5 mg)	2 years	Vitamin B treatment is effective on reducing brain atrophy in subjects with high plasma omega-3 fatty acids.
Van der Zwaluw, 2014 [125]	2919 older with Hcy	74,1	Folic acid µg 400 and Vitamin B12 µg 500	2 years	No beneficial effect on cognitive function.
Dysken, 2014 [126]	613 mild to moderate AD	65	Vitamin E 2 gr/day	5.2 months	Alpha tocopherol slowed functional decline in mild to moderate AD.
Aisen, 2008 [127]	340 AD and mild AD	75.7	5 mg/d of folate, 25 mg/d of vitamin B(6), 1 mg/d of vitamin B12	3.5 years	High-dose B vitamin supplements does not slow cognitive decline in individuals with mild to moderate AD.
Fillenburn, 2005 [51]	616 non-demented	73	Vitamin C and/or Vitamin E	14 years	Vitamins C and/or E did not delay the incidence of dementia or AD.
Ascherio, 2005 [128]	957.740 healthy	64.2	Vitamin E	10 years	Regular use of vitamin E supplements was associated with a lower risk of dying of ALS.

Hcy = homocisteine.

intervention is essential to prevent a faster cognitive decline in these patients [143]. The catabolic condition, as observed in the state of energy deficit, is harmful in patients with mild cognitive impairment or AD, causing a disease of cerebral starvation, also known as Type III diabetes [144].

In patients with mild cognitive impairment, a low BMI is correlated with an increased risk for AD progression [145,146] and this correlation is more evident in female, elderly and hypertensive subjects [147]. Furthermore, obesity and diabetes are associated with the development of AD [148]. This controversial result can be explained by the biological activity of insulin, deficient level in undernourished, and insulin-resistant in obese subjects, evidencing the critical role of insulin activity on brain function.

Ozawa et al. [65] in a prospective study conducted on a large population found that a reduced amount of rising and an increased vegetal and soybean intake was associated with a less incidence of dementia in the general population. However, in this study, no information was given about weight changes and metabolic parameter, and we cannot assume if the benefits induced by nutrition were correlated with the quality of diet or with reduced carbohydrates intake.

Marder et al. [66] in a prospective cohort study conducted on 1001 patients with HD controlled for nine months, found that MeDiet was not associated with motor symptoms onset. However, a higher food intake doubled the risk, probably due to a lower urate level, which is associated with a faster progression of motor symptoms in HD patients. Studies of diet and energy expenditure are necessary for premanifest HD to detect the specific macronutrients that may delay the onset and progression of is HD.

In patients with ALS, there a progressive decline of respiration, dysphagia, and consequent weight loss so that in some cases, gastrostomy feeding tubes can be useful [149]. Nutritional status, as assessed by the decrease in BMI, was negatively associated with disease severity using the ALSFRS-R (ALS Functional Rating Scale-Revised). The study suggested that the intake of nutrients decreases with disease progression in ALS patients [150]. A cross-sectional study conducted on a large population, the Amyotrophic Lateral Sclerosis Multicenter Cohort Study followed for 18 months, found that antioxidant intake with nutrient, fruit, and vegetables evaluated with a food questionnaire determined an improvement in physical and respiratory function [56]. Probiotics assumption had favorable effects on parameters of mental health, inflammatory markers, and insulin resistance, [83] in MS and AD [84] showing the involvement of gut microbiota in neurodegenerative diseases. Low-fat diets and antioxidant supplements may be used as complementary therapies for the treatment of MS [151].

In conclusion, the advantage of MedDiet in reducing the decline of cognitive function and memory could be related to the high polyphenols and antioxidant and low-fat content in the nutritional habit. Furthermore, a limited energy diet also contributes to improving insulin activity that is an essential regulator of the neuron function.

With a dose-response relationship [106]. Burckhardt et al. [152] in a recent meta-analysis did not find any positive evidence about the efficacy of omega-3 PUFA supplements in the treatment of mild to the moderate AD [54]. The effectiveness of PUFA administration on cognitive impairment and AD remains to be proved, and the efficiency found in some studies can be correlated with other metabolic components.

Possible mechanisms of action.

Polyphenols

Polyphenols have been demonstrated to be responsible for the anti-inflammatory and antioxidant properties of potentially functional foods. Polyphenolic compounds included in the various type of food have a significant protective effect on tissue metabolism, in particular on the brain. A new fool dietary polyphenol database is available [153]. Blueberries have the highest contents of polyphenols and have robust antioxidative benefits protecting mitochondrial function, and slowing the neurodegenerative process in PD [154] and AD inhibiting amyloid-β aggregation.

Resveratrol

A moderate intake of red wine (one glass per meal) represents one component of the beneficial effect of MedDiet due to resveratrol content [155,156] reducing the risk of dementia including AD [157]. Modest alcohol consumption (≤12.5 g/day) reduced the risk of dementia while excessive drinking (≥38 g/day) elevated the risk. [158]. Numerous in vitro and in vivo experimental models have shown that resveratrol reduced the amyloid formation [117], enhanced clearance of β-amyloid peptides [159,160], and exerted antioxidant properties [159]. The effect of resveratrol on the prevention of AD is relevant; however, if taken alone, may not be effective as single therapy [157]. Witte et al. [161] found that supplementation of resveratrol improved memory performance in association with improved glucose metabolism and the increased hippocampal area in older adults.

The mechanism of action of polyphenols on the amelioration of neurodegenerative diseases such as AD and PD, it not fully explained, but it seems that they regulate the aggregation and disaggregation of the amyloid peptide, tau, alpha-synuclein, synphilin-1, [160]. Importantly, resveratrol improves mitochondrial function against inflammation by activating sirtuin 1 (SIRT1) and PGC-1α [162]. Furthermore, resveratrol increases mitochondrial biogenesis and activity through the adenosine monophosphate-activated protein kinase (AMPK) and PGC-1α expression, [163]. The activation of the AMPK and SIRT1 expression inhibits the NF-kB inflammation pathways [164] showing a protective effect against senescence in response to environmental and pro-inflammatory stimuli [165,166]. Wang et al. [167] found that resveratrol inhibits β-amyloid fibrils formation reversing learning and memory disorders by the regulation of neuronal inflammation and apoptosis. Importantly, resveratrol is a modulator of estrogen receptors, and an anti-inflammatory effect on rats astrocytes and microglia was demonstrated [168]. This effect has been comparing to 17β-estradiol action, and the anti-NF-kB signal pathway may be one of the target mechanisms [168]. A cytoprotective action of resveratrol on human neuroblastoma cells exposed to β-amyloid and or β-amyloid-metal complex was also observed [169]. The activity of resveratrol mimics the effect of calorie restriction, increasing the levels and activity of SIRT1 (silent information regulator 2/sirtuin-1) that plays a central role in the body's response to diet and exercise [170].

Olive oil

The potential effect of olive oil to counteract neurological diseases has been extensively investigated in an animal model and humans. In mice, the administration of oleocanthal extracted from extra-virgin olive oil to C57BL/6 wild-type mice enhanced the β-amyloid clearance from the brain [125]. These experimental data support the potential preventive effect of extra-virgin olive oil on AD development by improving the β-amyloid clearance from the brain [171], regulating the antioxidant system with a beneficial effect on cognitive function [172]. It seems that oleocanthal acts as a natural anti-inflammatory compound strikingly similar to that of ibuprofen sharing pharmacologic properties. Although structurally dissimilar, both these molecules inhibit the same cyclooxygenase enzymes in the prostaglandin-biosynthesis pathway [173]. Olive oil contains a high rate of polyunsaturated omega-3 fatty acids, and almost more than thirteen can inhibit β-amyloid and tau aggregation and increasing their clearance by the brain, reducing the risk of AD [171]. In mice, long-term consumption of extra virgin olive oil contained in the diet, starting at an early age, provides a protective effect against the AD and its related disorder CAA [174]. The olive oil polyphenols have a beneficial effect reducing the incidence of chronic diseases such as cancer, cardiovascular, metabolic, and neurodegenerative diseases [175].

However, despite the positive effects of oleocanthal as a robust anti-inflammatory agent useful in neurodegenerative prevention, alone as a single therapeutic measure awaits validation from future studies [176]. More intervention studies need to be undertaken with longer study durations and larger sample sizes. It may prove fruitful to examine the effects of different doses as well as impact in other dementia subtypes [108].

Fruit and vegetables

Antioxidants, carotenes contained in fruits and vegetables have an anti-inflammatory effect and an enhanced immune cell response [177,178]. A diet rich in protein, fruits, and vegetables, together with moderate wine consumption would help to normalize the blood sugar giving protection against the development of ALS [179]. Higher intakes of fruits and vegetables led to both a reduction in pro-inflammatory mediators and an enhanced immune cell profile [177]. Higher legume and fish intake were associated with the larger cortical thickness [180].

Insulin signaling and calorie restriction (CR) effect

Hypercaloric diet with a high glycemic load had a negative in patients cognitively normal associated with a higher amyloid deposit in the brain [181]. A higher carbohydrates intake were significantly associated with the risk of ALS [25] and with higher amyloid deposition in the brain [181]. Reduction of calorie intake has a beneficial effect on health extending lifespan and exerting neuroprotection [182]. The long-term CR significantly reduced the cerebral amyloid deposition in a mouse model [183]. CR reduced age-related changes in the hippocampal neurons [184] and in the female mice reduced the gene expression of amyloid degeneration showing neuroprotective effects through an epigenetic mechanism [183]. Otherwise, Brownlow et al. [185] found no effect of the CR diet in mice on differences in the activation of astrocytes and microglia and no effect on spatial memory.

In obese patients, weight loss following a hypocaloric diet improved cardiometabolic and inflammatory risk factors [186]; but the long-term effect of a low-carbohydrate diet could be detrimental on endothelial function [187]. The impact of hypoenergy low-carbohydrate diet is the causal factor to improve plasma glucose level and insulin activity that, when abnormal, is harmful to brain health. The disruption of brain insulin signaling promotes the development and progression of AD [188], the reduction in hippocampal function and memory [189], in neuron activity, in synaptogenesis [190], favoring AD progression [191]. Insulin resistance favorites inflammation mitochondrial impairment play an essential role in neurodegenerative diseases [192,193]. The improved insulin activity exerts a crucial role against neurotoxicity, enhancing the dopamine action and up-regulating neurotrophic factors [194] while high-calorie diets may predispose to the neurodegenerative process age-related, particularly in persons with a genetic predisposition to such disorders [195]. Insulin signaling is very active in neurons, and glial function, and insulin resistance at brain level is involved in cognitive impairment and neuropathological abnormalities as observed in type-2 diabetes and obesity [196]. In humans, insulin resistance favorites the amyloid deposition in the brain zone affected by AD [197], and a correlation between type-2 diabetes and AD has been demonstrated [198–200]. The protein-tau is responsible for the insulin resistance in AD [201], and the hyperphosphorylated tau-bearing neurons is a causative factor for the insulin resistance [202]. In patients with metabolic syndrome, PET neuroimaging investigation showed an accelerated β-amyloid deposition in the brain [203]. Insulin signaling regulates phosphorylation of tau-protein, neuroinflammation, that are determinant components of AD [204]. An interaction between the genetic factor and insulin resistance has been found and provide evidence for new regulatory mechanisms that link type-2 diabetes and Alzheimer pathology [205].

Mechanistically, the hypocaloric diet leads to activation of SIRT1 and suppression of mTOR and S6K1 activation evidencing that this pathway may be involved in the neuroprotective effect of CR as observed in mice genetically modified (C57BL/6) [206]. The insulin/IGF1/PI3K/Akt signaling is involved in neurodegenerative disease as PD and AD [207]. PI3K/AKT pathway plays neuroprotection inhibiting apoptosis via the enhancing expression of the SODs. This pathway appears to be crucial in the AD because it is related to the protein-tau hyper-phosphorylation. Dietary intervention may provide a novel therapeutic approach to brain disorders by modulating the function of the PI3K/Akt pathway. The SODs and PI3K/Akt pathway play a significant role in the neuroprotective signaling against AD and PD[208]. The dysregulation of AMPK (a nutrient sensor) signaling in motor neurons is an early event in the pathogenesis of ALS, and an alteration in energy metabolism is considered a critical factor in the progression of ALS [209].

Ketogenic diet and brain function

The ketogenic dietary intervention consits in the reduction to a minimum carbohydrates intake (10% of daily calories), of associated to a very high-fat amount

(90% of total calorie intake) causing the ketones body formation [210] that can be detectable in the urine [211]. An average or high protein intake does not interact with ketones body formation [212]. The ketogenic diet is effective in improving the control of resistant epilepsy [213,214], and motor control [215]. Taylor et al. [216]found that the ketogenic diet in a small group of ten patients with AD, the cognitive scale (Alzheimer's Disease Assessment Scale) improved significantly. Ketogenic diet mitigates the neurodegeneration and enhances memory function. Ketone bodies are associated with glucose restriction have a protective effect on hippocampus contributing to seizure control and affecting DNA methylation [217]. Furthermore, it improves the electrical control of neurons [218], decreased apoptosis, and inflammation [219]. However, the ketogenic diet has a tremendous clinical limitation due to the side effect of fat intake.

Carbohydrate restriction associated with increased ingestion of medium-chain triglyceride induces a high ketone bodies formation, which improved brain function and memory in cognitive impairment and AD [220]. Neurocognitive function was enhanced by ketosis in a brief time after starting the ketogenic diet [221] and was associated with increased activity of the area of the hippocampus that mediates learning and semantic items. The metabolism of ketone bodies is energetically more efficient than glucose and protect neurons from oxidative glutamate toxicity [222], increasing mitochondrial energy generation [219,223], exerting an anti-hypoxia [224], and anti-inflammatory effect [219].

In rats, Wang et al. [225] found that the ketogenic diet had a neuroprotective function activating autophagy mediated by a reduction of mitochondrial cytochrome c release. The mechanism underlying the ketogenic diet appeared to be associated with the medium-chain triglyceride metabolism that directly inhibits AMPA receptors (glutamate receptors) and change the cell energetics through mitochondrial biogenesis [226]. Then, medium-chain fatty acids rather than ketones are likely involved in epilepsy and neuroprotection and in, and finding application in neurodegenerative diseases. Importantly, ketone bodies might mediate the neuroprotective effects as a mechanism similar to that observed after calorie restriction diet, underling that the mechanisms are similar, specifically at the mitochondrial level [219]. Furthermore, a high-fat diet alters the function of hippocampal astrocytes and glutamate transporters in mice activating the pathogenesis of metabolic brain disorders [227]. The mechanism of the beneficial action of a ketogenic diet on the brain remains to be elucidated. It should be investigated if, in ketogenic diet, are more effective the high ketone bodies or the low plasma level of insulin.

The gut-brain axis

Various microbial entities coexist in animal and human gastrointestinal trac, such as bacteria, fungi, and viruses which are globally called as gut 'microbiota' [228]. The hypothesis that gut microbiota can generate a signal that affects brain development and function and mental health is of increasing evidence [229]. Vice versa, brain disorders can negatively interfere on gut microbiota generating the 'gut brain-axis', involved in the progression of the neurodegenerative diseases [230]. The most abundant gut germs respectively are: Bacteroidetes, Firmicutes, Actinobacteria, Proteobacteria, and Verrucomicrobia, and the profile changes in many pathological conditions such as metabolic syndrome [231], neurodegenerative disease AD and PD [232], and irritable bowel syndrome [233]. Gut microbiota regulates the neuroinflammation process and alteration in its composition causes a strong alteration in autoimmune and inflammatory responses [234], and favoring the amyloid-β deposition in AD [235–237], and motor dysfunction in PD [236]. In mice model with MS, the regulation of gut dysbiosis reduced motor neuron dysfunction and axonal damage that were reversed after microbiota recolonization [238]. It seem that microbiota interact with the immune system activating CD4(+)CD39(+) T cells and CD5(+)CD1d(+) B cells [238] in the brain. Restoring a physiologic gut microbiota in AD patients the cognition improved [239,240] and oxidative stress in the brain decreased significantly activating SIRT-1 pathway [241]. A treatment with large-spectrum antibiotics reduced amyloid-β deposition improving neurological signs in AD mice model [242]. These studies demonstrated that the type of microorganism developed in the gut may activate or sustain the chronic disease.

An excessive presence of Firmicutes respect the Bacteroidetes has been considered responsible of an increased inflammatory condition in the gut and correlated with severe amyloid expression [243]. Short-chain fatty acids are reduced in the gut of PD patients and has been implicated in pathogenesis of PD [244]. Short-chain fatty acids are produced by bacterial fermentation, particularly by *Lachnospiraceae,* and have an antinflammatory effect; their depletion may activate microglial cell in the brain [236]. However, the reduction of short-chain fatty acids, is commonly observed in various illness [245], suggesting that this deficiency could be the consequence rather than the specific cause of the disease.

The gastrointestinal tract is connected to the brain through the lymphatic system [246] and another

important way of communication is represented by the vagal afferent fibers [247] activated by hormones secreted by gut cells such as serotonin, cholecystokinin, peptide YY, glucagon-like peptide-1, gherelin and oxitocyn. Bravo et al. [248] showed that chronic treatment with *Lactobacillus rhamnosus* reduced GABA mRNA in the brain *via vagus nerve* in the prefrontal cortex and amygdala. Despite the abundance of studies conducted on animal model, only a few conducted in human subjects are available. Hill-Burns, et al. [249] in a study conducted on 197 patients with PD found a significant alteration in gut microbiota. In in elderly patients with AD, Haran et al. [250] showed that the gut microbiota was characterized prevalently by bacteria with the ability to produce proinflammatory substances such as butyrate, and taxa. An abundant presence of Lactobacillaceae, Barnesiellaceae and Enterococcacea were found in PD patients [251]. Keshavarzian, et al. [252] showed in sigmoid mucosal biopsies collected from 38 PD patients that genes involved in lipopolysaccharide biosynthesis and type III bacterial secretion systems were significantly higher.

However, diet represent the most important influencer of the microbiota composition throughout the life [253,254]. The western diet with restricted carbohydrates intake is responsible of a reduced production of gut microbiota and of short-chain fatty acids [255]. The variations in the diet induce alterations in gut microbiota in a short time [256]. Changes in macronutrients ingestion represent an important physiological regulator of the gut microbiota and also of the expression of genes and proteins [257].

In conclusion, alterations in gut microbiota are responsible of an inflammatory state in the bowel and increase cytokines production that exacerbate the neurodegenerative process in brain. A healthy dietary strategy characterize by macronutrients equilibrium may improve neurocognition and reduce the progression of the diseases. However, the alteration of gut microbiota may be a consequence of malnutrition rather than the primary cause.

Effect of dietary composition

The effect of macronutrients of the diet exerts a powerful impact of longevity compared to CR, when compared to a low-protein high-carbohydrates diet [258]. The nutrient-sensing pathways causing/linking longevity include SIRT1, the mechanistic target of rapamycin (mTOR), AMPK, insulin/IGF1, and FGF21 (fibroblast growth factor 21) [259,260]. However, diet induces complex metabolic changes and it has been debated if longevity is a consequence of CR intervention or dependent on the reduction of one macronutrient, [261]. In particular has been demonstrated that dietary protein intake has the most substantial impact on food intake, such as low protein diet that could lead to increased food intake and vice-versa; this phenomenon has termed 'protein leverage' [262].

High protein diet and ketogenic diet seem to be effective in increasing the IGF-1 plasma level and stimulating the IGF-1 receptor expression in the brain [263]. Circulating IGF-1 level has a protective effect on the brain and mediates the formation of new neurons in the adult hippocampus [264] has a neuroprotective effect [265]. So that favoring lower insulin and higher IGF-1 plasma level has a protective effect on the neuron, and a low carbohydrate-high protein diet seems to support this hormonal attitude. A high-fat diet predisposes to neuroinflammation in central and peripheral nervous systems and AD.

Future perspectives

Nutrition plays a protective effect on neuron integrity through the interaction of various components such as the quality of diet, the calorie intake, and the impact on insulin secretion. Insulin resistance is detrimental to neuron function, due to its activation of pro-inflammatory cytokines secretion. Clinical studies, with the attempt to evaluate the effect of the nutrition on neurodegenerative diseases, should take into account also of calorie ingestion and insulin sensitivity, as an essential marker of cellular function, and body weight change. Nutritional restriction, but also energy expenditure, is an important determinant factor in the evolution of neurodegenerative diseases [266]. Regulation of gut microbiota is important in the control of neurodegenerative diseases and in perspective, the hypothesis of fecal transplantation of selected microbiota in the treatment of neurodegenerative disease may be considered as a novel therapeutic strategy.

Specific cause-effect relationship on large populations in long term studies to evaluate the correlation between nutrition and disease progression are still lacking.

Conclusion

Nutrition represents an important strategy to prevent the neuronal and cognitive decline in neurodegenerative diseases (Figure 2). MeDiet reduces AD and PD progression due to the high intake of polyphenols and reduced calorie ingestion. Cognitive deterioration seems more correlated with the improvement of insulin action in the brain. A high-glycemic diet correlated with a higher incidence of the AD. A low carbohydrate-high

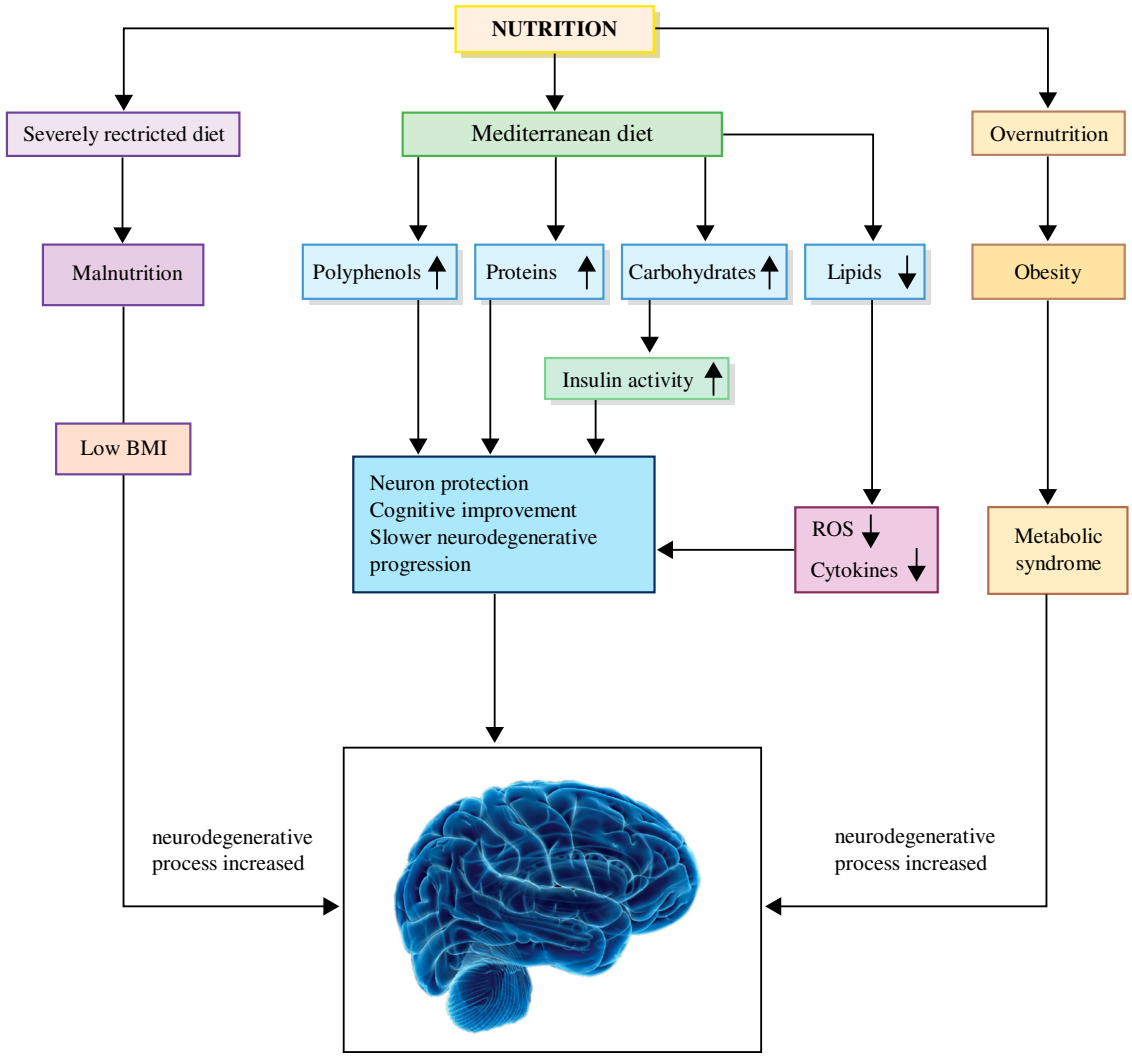

Figure 2. Nutrition can affect brain function and neurodegenerative process profoundly. Low intake of nutrients induces a malnutritional condition, with low BMI increasing the neurodegenerative process. Differently, overnutrition can generate obesity and metabolic syndrome, which is also responsible of neurodegeneration due to insulin resistance and inflammatory markers. Mediterranean diet, due to the controlled caloric intake, polyphenol and flavonoids (fruit, vegetables, olive oil, red wine) plus a regular intake of protein (fish and meets) and carbohydrates (cereals) reduces the insulin resistance and the pro-inflammatory cytokines level determining neuronal protection and slowering neuorodegenerative progression.

protein diet supports this hormonal attitude while a high-fat diet predisposes to neuroinflammation in central and peripheral nervous systems. Undernutrition has a deleterious effect on the evolution and mortality of neurodegenerative diseases, and patients with low BMI have a higher risks.

The administration of polyunsaturated fatty acids, either alone or in combination, had no significant effects on cognitive decline. high-dose B vitamin supplementation seemed beneficial in patients with cognitive dysfunction. Dietary supplementation with protein showed a positive effect on cognitive function.

The clinical effects of nutrition on neurodegenerative diseases should be evaluated including energy and macronutrients intake and plasma insulin and IGF-1level.

Disclosure statement

No potential conflict of interest was reported by the authors.

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References

[1] Barnes DE, Yaffe K. The projected effect of risk factor reduction on Alzheimer's disease prevalence. Lancet Neurol. 2011;10(9):819–28.

[2] Lardenoije R, van den Hove DLA, Havermans M, van Casteren A, Le KX, Palmour R, et al. Age-related

epigenetic changes in hippocampal subregions of four animal models of Alzheimer's disease. Mol Cell Neurosci. 2018;86:1–15.
[3] Reitz C, Mayeux R. Alzheimer disease: epidemiology, diagnostic criteria, risk factors and biomarkers. Biochem Pharmacol. 2014;88(4):640–51.
[4] Mayeux R, Stern Y. Epidemiology of Alzheimer disease. Cold Spring Harb Perspect Med. 2012;2(8).
[5] Niu H, Alvarez-Alvarez I, Guillen-Grima F, Al-Rahamneh MJ, Aguinaga-Ontoso I. Trends of mortality from Alzheimer's disease in the European Union, 1994-2013. Eur J Neurol. 2017;24(6):858–66.
[6] Baig SS, Strong M, Quarrell OW. The global prevalence of Huntington's disease: a systematic review and discussion. Neurodegener Dis Manag. 2016;6 (4):331–43.
[7] Shimizu T, Nagaoka U, Nakayama Y, Kawata A, Kugimoto C, Kuroiwa Y, et al. Reduction rate of body mass index predicts prognosis for survival in amyotrophic lateral sclerosis: a multicenter study in Japan. Amyotroph Lateral Scler. 2012;13(4):363–6.
[8] Ikeda M, Brown J, Holland AJ, Fukuhara R, Hodges JR. Changes in appetite, food preference, and eating habits in frontotemporal dementia and Alzheimer's disease. J Neurol Neurosurg Psychiatry. 2002;73(4):371–6.
[9] Droogsma E, van Asselt D, De Deyn PP. Weight loss and undernutrition in community-dwelling patients with Alzheimer's dementia: from population based studies to clinical management. Z Gerontol Geriatr. 2015;48(4):318–24.
[10] Hsu DC, Mormino EC, Schultz AP, Amariglio RE, Donovan NJ, Rentz DM, et al. Lower late-life body-mass index is associated with higher cortical amyloid burden in clinically normal elderly. J Alzheimers Dis. 2016;53(3):1097–105.
[11] Herrup K. Reimagining Alzheimer's disease–an age-based hypothesis. J Neurosci. 2010;30(50):16755–62.
[12] Tenkorang MA, Snyder B, Cunningham RL. Sex-related differences in oxidative stress and neurodegeneration. Steroids. 2018;133:21–7.
[13] Gratwicke J, Jahanshahi M, Foltynie T. Parkinson's disease dementia: a neural networks perspective. Brain. 2015;138(Pt 6):1454–76.
[14] Bohnen NI, Kaufer DI, Ivanco LS, Lopresti B, Koeppe RA, Davis JG, et al. Cortical cholinergic function is more severely affected in parkinsonian dementia than in Alzheimer disease: an in vivo positron emission tomographic study. Arch Neurol. 2003;60(12):1745–8.
[15] Ashraghi MR, Pagano G, Polychronis S, Niccolini F, Politis M. Parkinson's disease, diabetes and cognitive impairment. Recent Pat Endocr Metab Immune Drug Discov. 2016;10(1):11–21.
[16] Bosco D, Plastino M, Cristiano D, Colica C, Ermio C, De Bartolo M, et al. Dementia is associated with insulin resistance in patients with Parkinson's disease. J Neurol Sci. 2012;315(1-2):39–43.
[17] Oh J, An JW, Oh SI, Oh KW, Kim JA, Lee JS, et al. Socioeconomic costs of amyotrophic lateral sclerosis according to staging system. Amyotroph Lateral Scler Frontotemporal Degener. 2015;16(3-4):202–8.
[18] del Aguila MA, Longstreth WT, McGuire V, Koepsell TD, van Belle G. Prognosis in amyotrophic lateral sclerosis: a population-based study. Neurology. 2003;60(5):813–9.
[19] Arthur KC, Calvo A, Price TR, Geiger JT, Chio A, Traynor BJ. Projected increase in amyotrophic lateral sclerosis from 2015 to 2040. Nat Commun. 2016;7:12408.
[20] Ferraiuolo L, Kirby J, Grierson AJ, Sendtner M, Shaw PJ. Molecular pathways of motor neuron injury in amyotrophic lateral sclerosis. Nat Rev Neurol. 2011;7 (11):616–30.
[21] Riancho J, Bosque-Varela P, Perez-Pereda S, Povedano M, de Munain AL, Santurtun A. The increasing importance of environmental conditions in amyotrophic lateral sclerosis. Int J Biometeorol. 2018;62(8):1361–74.
[22] Celeste DB, Miller MS. Reviewing the evidence for viruses as environmental risk factors for ALS: a new perspective. Cytokine. 2018;108:173–8.
[23] Joardar A, Manzo E, Zarnescu DC. Metabolic dysregulation in amyotrophic lateral sclerosis: challenges and Opportunities. Curr Genet Med Rep. 2017;5 (2):108–14.
[24] D'Amico E, Factor-Litvak P, Santella RM, Mitsumoto H. Clinical perspective on oxidative stress in sporadic amyotrophic lateral sclerosis. Free Radic Biol Med. 2013;65:509–27.
[25] Okamoto K, Kihira T, Kondo T, Kobashi G, Washio M, Sasaki S, et al. Nutritional status and risk of amyotrophic lateral sclerosis in Japan. Amyotroph Lateral Scler. 2007;8(5):300–4.
[26] O'Reilly EJ, Wang H, Weisskopf MG, Fitzgerald KC, Falcone G, McCullough ML, et al. Premorbid body mass index and risk of amyotrophic lateral sclerosis. Amyotroph Lateral Scler Frontotemporal Degener. 2013;14(3):205–11.
[27] Paganoni S, Deng J, Jaffa M, Cudkowicz ME, Wills AM. Body mass index, not dyslipidemia, is an independent predictor of survival in amyotrophic lateral sclerosis. Muscle Nerve. 2011;44(1):20–4.
[28] Ahmed RM, Caga J, Devenney E, Hsieh S, Bartley L, Highton-Williamson E, et al. Cognition and eating behavior in amyotrophic lateral sclerosis: effect on survival. J Neurol. 2016;263(8):1593–603.
[29] Traynor BJ, Codd MB, Corr B, Forde C, Frost E, Hardiman OM. Clinical features of amyotrophic lateral sclerosis according to the El Escorial and Airlie House diagnostic criteria: a population-based study. Arch Neurol. 2000;57(8):1171–6.
[30] Robberecht W, Philips T. The changing scene of amyotrophic lateral sclerosis. Nat Rev Neurosci. 2013;14 (4):248–64.
[31] Karussis D. The diagnosis of multiple sclerosis and the various related demyelinating syndromes: a critical review. J Autoimmun. 2014;48-49:134–42.
[32] Dutta R, Trapp BD. Relapsing and progressive forms of multiple sclerosis: insights from pathology. Curr Opin Neurol. 2014;27(3):271–8.
[33] Grytten N, Torkildsen O, Myhr KM. Time trends in the incidence and prevalence of multiple sclerosis in Norway during eight decades. Acta Neurol Scand. 2015;132(199):29–36.
[34] Browne P, Chandraratna D, Angood C, Tremlett H, Baker C, Taylor BV, et al. Atlas of multiple sclerosis

2013: a growing global problem with widespread inequity. Neurology. 2014;83(11):1022–4.
[35] Passos GR D, Sato DK, Becker J, Fujihara K. Th17 cells pathways in multiple sclerosis and neuromyelitis optica spectrum disorders: pathophysiological and therapeutic implications. Mediators Inflamm. 2016; 2016:5314541.
[36] Wu H, Zhao M, Yoshimura A, Chang C, Lu Q. Critical link between epigenetics and transcription factors in the induction of autoimmunity: a comprehensive review. Clin Rev Allergy Immunol. 2016;50(3):333–44.
[37] McLeod JG, Hammond SR, Kurtzke JF. Migration and multiple sclerosis in United Kingdom and Ireland immigrants to Australia: a reassessment. II. characteristics of early (pre-1947) compared to later migrants. J Neurol. 2012;259(4):684–93.
[38] Riemann-Lorenz K, Eilers M, von Geldern G, Schulz KH, Kopke S, Heesen C. Dietary interventions in multiple sclerosis: development and pilot-testing of an evidence based patient education program. PLoS One. 2016;11(10):e0165246.
[39] Farinotti M, Vacchi L, Simi S, Di Pietrantonj C, Brait L, Filippini G. Dietary interventions for multiple sclerosis. Cochrane Database Syst Rev. 2012;12: CD004192.
[40] Landles C, Bates GP. Huntingtin and the molecular pathogenesis of Huntington's disease. Fourth in molecular medicine review series. EMBO Rep. 2004;5 (10):958–63.
[41] Sharma S, Taliyan R. Transcriptional dysregulation in Huntington's disease: the role of histone deacetylases. Pharmacol Res. 2015;100:157–69.
[42] Ehrnhoefer DE, Butland SL, Pouladi MA, Hayden MR. Mouse models of Huntington disease: variations on a theme. Dis Model Mech. 2009;2(3-4):123–9.
[43] Damiano M, Galvan L, Deglon N, Brouillet E. Mitochondria in Huntington's disease. Biochim Biophys Acta. 2010;1802(1802):52–61.
[44] Sussmuth SD, Muller VM, Geitner C, Landwehrmeyer GB, Iff S, Gemperli A, et al. Fat-free mass and its predictors in Huntington's disease. J Neurol. 2015;262 (6):1533–40.
[45] Jucker M, Walker LC. Pathogenic protein seeding in Alzheimer disease and other neurodegenerative disorders. Ann Neurol. 2011;70(4):532–40.
[46] Ross CA, Poirier MA. Protein aggregation and neurodegenerative disease. Nat Med. 2004;(10 Suppl):S10–7.
[47] Manoharan S, Guillemin GJ, Abiramasundari RS, Essa MM, Akbar M, Akbar MD. The role of reactive oxygen species in the pathogenesis of Alzheimer's disease, Parkinson's disease, and huntington's disease: a mini review. Oxid Med Cell Longev. 2016;2016:8590578.
[48] Liang JH, Xu Y, Lin L, Jia RX, Zhang HB, Hang L. Comparison of multiple interventions for older adults with Alzheimer disease or mild cognitive impairment: a PRISMA-compliant network meta-analysis. Medicine (Baltimore. 2018;97(20):e10744.
[49] Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gotzsche PC, Ioannidis JP, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. PLoS Med. 2009;6(7):e1000100.
[50] Young KW, Greenwood CE, van Reekum R, Binns MA. Providing nutrition supplements to institutionalized seniors with probable Alzheimer's disease is least beneficial to those with low body weight status. J Am Geriatr Soc. 2004;52(8):1305–12.
[51] Fillenbaum GG, Kuchibhatla MN, Hanlon JT, Artz MB, Pieper CF, Schmader KE, et al. Dementia and Alzheimer's disease in community-dwelling elders taking vitamin C and/or vitamin E. Ann Pharmacother. 2005;39 (12):2009–14.
[52] Remington R, Bechtel C, Larsen D, Samar A, Page R, Morrell C, et al. Maintenance of cognitive performance and mood for individuals with Alzheimer's disease following consumption of a nutraceutical formulation: a one-year, open-label study. J Alzheimers Dis. 2016;51 (4):991–5.
[53] Rotstein DL, Cortese M, Fung TT, Chitnis T, Ascherio A, Munger KL. Diet quality and risk of multiple sclerosis in two cohorts of US women. Mult Scler. 2018.
[54] Baleztena J, Ruiz-Canela M, Sayon-Orea C, Pardo M, Anorbe T, Gost JI, et al. Association between cognitive function and supplementation with omega-3 PUFAs and other nutrients in >/ = 75 years old patients: a randomized multicenter study. PLoS One. 2018;13(3): e0193568.
[55] Berti V, Walters M, Sterling J, Quinn CG, Logue M, Andrews R, et al. Mediterranean diet and 3-year Alzheimer brain biomarker changes in middle-aged adults. Neurology. 2018;90(20):e1789–e98.
[56] Nieves JW, Gennings C, Factor-Litvak P, Hupf J, Singleton J, Sharf V, et al. Association between dietary intake and function in amyotrophic lateral sclerosis. JAMA Neurol. 2016;73(12):1425–32.
[57] Anastasiou CA, Yannakoulia M, Kosmidis MH, Dardiotis E, Hadjigeorgiou GM, Sakka P, et al. Mediterranean diet and cognitive health: initial results from the hellenic longitudinal investigation of ageing and diet. PLoS One. 2017;12(8):e0182048.
[58] Knight A, Bryan J, Wilson C, Hodgson JM, Davis CR, Murphy KJ. The Mediterranean diet and cognitive function among healthy older adults in a 6-month randomised controlled trial: the MedLey study. Nutrients. 2016;8(9.
[59] Olsson E, Karlstrom B, Kilander L, Byberg L, Cederholm T, Sjogren P. Dietary patterns and cognitive dysfunction in a 12-year follow-up study of 70 year old men. J Alzheimers Dis. 2015;43(1):109–19.
[60] Qin B, Adair LS, Plassman BL, Batis C, Edwards LJ, Popkin BM, et al. Dietary patterns and cognitive decline Among Chinese older adults. Epidemiology. 2015;26 (5):758–68.
[61] Trichopoulou A, Kyrozis A, Rossi M, Katsoulis M, Trichopoulos D, La Vecchia C, et al. Mediterranean diet and cognitive decline over time in an elderly Mediterranean population. Eur J Nutr. 2015;54 (8):1311–21.
[62] Valls-Pedret C, Sala-Vila A, Serra-Mir M, Corella D, de la Torre R, Martinez-Gonzalez MA, et al. Mediterranean diet and age-related cognitive decline: a randomized clinical trial. JAMA Intern Med. 2015;175(7):1094–103.
[63] Zbeida M, Goldsmith R, Shimony T, Vardi H, Naggan L, Shahar DR. Mediterranean diet and functional

indicators among older adults in non-Mediterranean and Mediterranean countries. J Nutr Health Aging. 2014;18(4):411–8.
[64] Mosconi L, Murray J, Tsui WH, Li Y, Davies M, Williams S, et al. Mediterranean diet and magnetic resonance imaging-assessed brain atrophy in cognitively normal individuals at risk for Alzheimer's disease. J Prev Alzheimers Dis. 2014;1(1):23–32.
[65] Ozawa M, Ninomiya T, Ohara T, Doi Y, Uchida K, Shirota T, et al. Dietary patterns and risk of dementia in an elderly Japanese population: the Hisayama study. Am J Clin Nutr. 2013;97(5):1076–82.
[66] Marder K, Gu Y, Eberly S, Tanner CM, Scarmeas N, Oakes D, et al. Relationship of Mediterranean diet and caloric intake to phenoconversion in Huntington disease. JAMA Neurol. 2013;70(11):1382–8.
[67] Martinez-Lapiscina EH, Clavero P, Toledo E, Estruch R, Salas-Salvado J, San Julian B, et al. Mediterranean diet improves cognition: the PREDIMED-NAVARRA randomised trial. J Neurol Neurosurg Psychiatry. 2013;84(12):1318–25.
[68] Kesse-Guyot E, Andreeva VA, Lassale C, Ferry M, Jeandel C, Hercberg S, et al. Mediterranean diet and cognitive function: a French study. Am J Clin Nutr. 2013;97(2):369–76.
[69] Ye X, Scott T, Gao X, Maras JE, Bakun PJ, Tucker KL. Mediterranean diet, healthy eating index 2005, and cognitive function in middle-aged and older Puerto Rican adults. J Acad Nutr Diet. 2013;113(2):276–81 e1-3.
[70] Tsivgoulis G, Judd S, Letter AJ, Alexandrov AV, Howard G, Nahab F, et al. Adherence to a Mediterranean diet and risk of incident cognitive impairment. Neurology. 2013;80(18):1684–92.
[71] Samieri C, Grodstein F, Rosner BA, Kang JH, Cook NR, Manson JE, et al. Mediterranean diet and cognitive function in older age. Epidemiology. 2013; 24(4):490–9.
[72] Cherbuin N, Anstey KJ. The Mediterranean diet is not related to cognitive change in a large prospective investigation: the PATH through life study. Am J Geriatr Psychiatry. 2012;20(7):635–9.
[73] Vercambre MN, Grodstein F, Berr C, Kang JH. Mediterranean diet and cognitive decline in women with cardiovascular disease or risk factors. J Acad Nutr Diet. 2012;112(6):816–23.
[74] Tangney CC, Kwasny MJ, Li H, Wilson RS, Evans DA, Morris MC. Adherence to a Mediterranean-type dietary pattern and cognitive decline in a community population. Am J Clin Nutr. 2011;93(3):601–7.
[75] Gu Y, Brickman AM, Stern Y, Habeck CG, Razlighi QR, Luchsinger JA, et al. Mediterranean diet and brain structure in a multiethnic elderly cohort. Neurology. 2015;85(20):1744–51.
[76] Feart C, Samieri C, Rondeau V, Amieva H, Portet F, Dartigues JF, et al. Adherence to a Mediterranean diet, cognitive decline, and risk of dementia. JAMA. 2009;302(6):638–48.
[77] Scarmeas N, Stern Y, Mayeux R, Manly JJ, Schupf N, Luchsinger JA. Mediterranean diet and mild cognitive impairment. Arch Neurol. 2009;66(2):216–25.
[78] Scarmeas N, Luchsinger JA, Mayeux R, Stern Y. Mediterranean diet and Alzheimer disease mortality. Neurology. 2007;69(11):1084–93.
[79] Wengreen H, Munger RG, Cutler A, Quach A, Bowles A, Corcoran C, et al. Prospective study of dietary approaches to Stop hypertension- and Mediterranean-style dietary patterns and age-related cognitive change: the cache county study on memory, health and aging. Am J Clin Nutr. 2013;98(5):1263–71.
[80] Gardener S, Gu Y, Rainey-Smith SR, Keogh JB, Clifton PM, Mathieson SL, et al. Adherence to a Mediterranean diet and Alzheimer's disease risk in an Australian population. Transl Psychiatry. 2012;2:e164.
[81] Gu Y, Luchsinger JA, Stern Y, Scarmeas N. Mediterranean diet, inflammatory and metabolic biomarkers, and risk of Alzheimer's disease. J Alzheimers Dis. 2010;22(2):483–92.
[82] Tamtaji OR, Heidari-Soureshjani R, Mirhosseini N, Kouchaki E, Bahmani F, Aghadavod E, et al. Probiotic and selenium co-supplementation, and the effects on clinical, metabolic and genetic status in Alzheimer's disease: a randomized, double-blind, controlled trial. Clin Nutr. 2018;12:S0261–5614.
[83] Kouchaki E, Tamtaji OR, Salami M, Bahmani F, Daneshvar Kakhaki R, Akbari E, et al. Clinical and metabolic response to probiotic supplementation in patients with multiple sclerosis: a randomized, double-blind, placebo-controlled trial. Clin Nutr. 2017;36(5):1245–9.
[84] Akbari E, Asemi Z, Daneshvar Kakhaki R, Bahmani F, Kouchaki E, Tamtaji OR, et al. Effect of probiotic supplementation on cognitive function and metabolic status in Alzheimer's disease: a randomized, double-blind and controlled trial. Front Aging Neurosci. 2016;8:256.
[85] van der Zwaluw NL, van de Rest O, Tieland M, Adam JJ, Hiddink GJ, van Loon LJ, et al. The impact of protein supplementation on cognitive performance in frail elderly. Eur J Nutr. 2014;53(3):803–12.
[86] Remington R, Lortie JJ, Hoffmann H, Page R, Morrell C, Shea TB. A nutritional formulation for cognitive performance in mild cognitive impairment: a placebo-controlled trial with an open-label extension. J Alzheimers Dis. 2015;48(3):591–5.
[87] Suominen MH, Puranen TM, Jyvakorpi SK, Eloniemi-Sulkava U, Kautiainen H, Siljamaki-Ojansuu U, et al. Nutritional guidance improves nutrient intake and quality of life, and may prevent falls in aged persons with Alzheimer disease living with a Spouse (NuAD trial). J Nutr Health Aging. 2015;19(9):901–7.
[88] Sheard JM, Ash S, Mellick GD, Silburn PA, Kerr GK. Improved nutritional status is related to improved quality of life in Parkinson's disease. BMC Neurol. 2014;14:212.
[89] Kwok TC, Lam LC, Sea MM, Goggins W, Woo J. A randomized controlled trial of dietetic interventions to prevent cognitive decline in old age hostel residents. Eur J Clin Nutr. 2012;66(10):1135–40.
[90] Jyvakorpi SK, Puranen T, Pitkala KH, Suominen MH. Nutritional treatment of aged individuals with Alzheimer disease living at home with their spouses:

study protocol for a randomized controlled trial. Trials. 2012;13:66.
[91] Pivi GA, da Silva RV, Juliano Y, Novo NF, Okamoto IH, Brant CQ, et al. A prospective study of nutrition education and oral nutritional supplementation in patients with Alzheimer's disease. Nutr J. 2011;10:98.
[92] Salva A, Andrieu S, Fernandez E, Schiffrin EJ, Moulin J, Decarli B, et al. Health and nutritional promotion program for patients with dementia (NutriAlz study): design and baseline data. J Nutr Health Aging. 2009;13(6):529–37.
[93] Salas-Salvado J, Torres M, Planas M, Altimir S, Pagan C, Gonzalez ME, et al. Effect of oral administration of a whole formula diet on nutritional and cognitive status in patients with Alzheimer's disease. Clin Nutr. 2005;24 (3):390–7.
[94] Trejo A, Boll MC, Alonso ME, Ochoa A, Velasquez L. Use of oral nutritional supplements in patients with Huntington's disease. Nutrition. 2005;21(9):889–94.
[95] Lauque S, Arnaud-Battandier F, Gillette S, Plaze JM, Andrieu S, Cantet C, et al. Improvement of weight and fat-free mass with oral nutritional supplementation in patients with Alzheimer's disease at risk of malnutrition: a prospective randomized study. J Am Geriatr Soc. 2004;52(10):1702–7.
[96] Gil Gregorio P, Ramirez Diaz SP, Ribera Casado JM. group D. dementia and nutrition. intervention study in institutionalized patients with Alzheimer disease. J Nutr Health Aging. 2003;7(5):304–8.
[97] Riviere S, Gillette-Guyonnet S, Voisin T, Reynish E, Andrieu S, Lauque S, et al. A nutritional education program could prevent weight loss and slow cognitive decline in Alzheimer's disease. J Nutr Health Aging. 2001;5(4):295–9.
[98] Soininen H, Solomon A, Visser PJ, Hendrix SB, Blennow K, Kivipelto M, et al. 24-month intervention with a specific multinutrient in people with prodromal Alzheimer's disease (LipiDiDiet): a randomised, double-blind, controlled trial. Lancet Neurol. 2017;16 (12):965–75.
[99] Salva A, Andrieu S, Fernandez E, Schiffrin EJ, Moulin J, Decarli B, et al. Health and nutrition promotion program for patients with dementia (NutriAlz): cluster randomized trial. J Nutr Health Aging. 2011;15 (10):822–30.
[100] Tamtaji OR, Taghizadeh M, Daneshvar Kakhaki R, Kouchaki E, Bahmani F, Borzabadi S, et al. Clinical and metabolic response to probiotic administration in people with Parkinson's disease: a randomized, double-blind, placebo-controlled trial. Clin Nutr. 2019;38(3):1031–5.
[101] Andrieu S, Guyonnet S, Coley N, Cantet C, Bonnefoy M, Bordes S, et al. Effect of long-term omega 3 polyunsaturated fatty acid supplementation with or without multidomain intervention on cognitive function in elderly adults with memory complaints (MAPT): a randomised, placebo-controlled trial. Lancet Neurol. 2017;16(5):377–89.
[102] Mazereeuw G, Herrmann N, Oh PI, Ma DW, Wang CT, Kiss A, et al. Omega-3 fatty acids, depressive symptoms, and cognitive performance in patients with coronary Artery disease: analyses from a randomized, double-blind, placebo-controlled trial. J Clin Psychopharmacol. 2016;36(5):436–44.
[103] Zhang Y, Chen J, Qiu J, Li Y, Wang J, Jiao J. Intakes of fish and polyunsaturated fatty acids and mild-to-severe cognitive impairment risks: a dose-response meta-analysis of 21 cohort studies. Am J Clin Nutr. 2015;103(2):330–40.
[104] Jackson PA, Forster JS, Bell JG, Dick JR, Younger I, Kennedy DO. Dha supplementation alone or in combination with other nutrients does not Modulate cerebral Hemodynamics or cognitive function in healthy older adults. Nutrients. 2016;8(2):86.
[105] Kulzow N, Witte AV, Kerti L, Grittner U, Schuchardt JP, Hahn A, et al. Impact of omega-3 fatty acid supplementation on memory functions in healthy older adults. J Alzheimers Dis. 2016;51(3):713–25.
[106] Eriksdotter M, Vedin I, Falahati F, Freund-Levi Y, Hjorth E, Faxen-Irving G, et al. Plasma fatty acid profiles in relation to cognition and gender in Alzheimer's disease patients During oral omega-3 fatty acid supplementation: the OmegAD study. J Alzheimers Dis. 2015;48(3):805–12.
[107] Chew EY, Clemons TE, Agron E, Launer LJ, Grodstein F, Bernstein PS, et al. Effect of omega-3 fatty acids, lutein/zeaxanthin, or other nutrient supplementation on cognitive function: the AREDS2 randomized clinical trial. JAMA. 2015;314(8):791–801.
[108] Phillips MA, Childs CE, Calder PC, Rogers PJ. No effect of omega-3 fatty acid supplementation on cognition and mood in individuals with cognitive impairment and probable Alzheimer's disease: a randomised controlled trial. Int J Mol Sci. 2015;16(10):24600–13.
[109] Geleijnse JM, Giltay EJ, Kromhout D. Effects of n-3 fatty acids on cognitive decline: a randomized, double-blind, placebo-controlled trial in stable myocardial infarction patients. Alzheimers Dement. 2012;8(4):278–87.
[110] Jaremka LM, Derry HM, Bornstein R, Prakash RS, Peng J, Belury MA, et al. Omega-3 supplementation and loneliness-related memory problems: secondary analyses of a randomized controlled trial. Psychosom Med. 2014;76(8):650–8.
[111] Witte AV, Kerti L, Hermannstadter HM, Fiebach JB, Schreiber SJ, Schuchardt JP, et al. Long-chain omega-3 fatty acids improve brain function and structure in older adults. Cereb Cortex. 2014;24(11):3059–68.
[112] Mahmoudi MJ, Hedayat M, Sharifi F, Mirarefin M, Nazari N, Mehrdad N, et al. Effect of low dose omega-3 poly unsaturated fatty acids on cognitive status among older people: a double-blind randomized placebo-controlled study. J Diabetes Metab Disord. 2014;13(1):34.
[113] Yurko-Mauro K, McCarthy D, Rom D, Nelson EB, Ryan AS, Blackwell A, et al. Beneficial effects of docosahexaenoic acid on cognition in age-related cognitive decline. Alzheimers Dement. 2010;6(6):456–64.
[114] van de Rest O, Geleijnse JM, Kok FJ, van Staveren WA, Dullemeijer C, Olderikkert MG, et al. Effect of fish oil on cognitive performance in older subjects: a randomized, controlled trial. Neurology. 2008;71(6):430–8.
[115] Freund-Levi Y, Eriksdotter-Jonhagen M, Cederholm T, Basun H, Faxen-Irving G, Garlind A, et al. Omega-3 fatty acid treatment in 174 patients with mild to

moderate Alzheimer disease: OmegAD study: a randomized double-blind trial. Arch Neurol. 2006;63 (10):1402–8.
[116] Jerneren F, Elshorbagy AK, Oulhaj A, Smith SM, Refsum H, Smith AD. Brain atrophy in cognitively impaired elderly: the importance of long-chain omega-3 fatty acids and B vitamin status in a randomized controlled trial. Am J Clin Nutr. 2015;102(1):215–21.
[117] Regitz C, Fitzenberger E, Mahn FL, Dussling LM, Wenzel U. Resveratrol reduces amyloid-beta (Abeta (1)(-)(4)(2))-induced paralysis through targeting proteostasis in an Alzheimer model of Caenorhabditis elegans. Eur J Nutr. 2016;55(2):741–7.
[118] Yip PK, Pizzasegola C, Gladman S, Biggio ML, Marino M, Jayasinghe M, et al. The omega-3 fatty acid eicosapentaenoic acid accelerates disease progression in a model of amyotrophic lateral sclerosis. PLoS One. 2013;8(4):e61626.
[119] Kwok T, Lee J, Ma RC, Wong SY, Kung K, Lam A, et al. A randomized placebo controlled trial of vitamin B12 supplementation to prevent cognitive decline in older diabetic people with borderline low serum vitamin B12. Clin Nutr. 2017;36(6):1509–15.
[120] Liu G, Zhao Y, Jin S, Hu Y, Wang T, Tian R, et al. Circulating vitamin E levels and Alzheimer's disease: a Mendelian randomization study. Neurobiol Aging. 2018;72:189 e1–e9.
[121] Hiller AL, Murchison CF, Lobb BM. O'Connor S, O'Connor M, Quinn JF. A randomized, controlled pilot study of the effects of vitamin D supplementation on balance in Parkinson's disease: does age matter? PLoS One. 2018;13(9):e0203637.
[122] Kryscio RJ, Abner EL, Caban-Holt A, Lovell M, Goodman P, Darke AK, et al. Association of antioxidant supplement Use and dementia in the prevention of Alzheimer's disease by vitamin E and selenium trial (PREADViSE). JAMA Neurol. 2017;74 (5):567–73.
[123] Chen H, Liu S, Ji L, Wu T, Ji Y, Zhou Y, et al. Folic acid supplementation mitigates Alzheimer's disease by reducing inflammation: a randomized controlled trial. Mediators Inflamm. 2016;2016:5912146.
[124] Dangour AD, Allen E, Clarke R, Elbourne D, Fletcher AE, Letley L, et al. Effects of vitamin B-12 supplementation on neurologic and cognitive function in older people: a randomized controlled trial. Am J Clin Nutr. 2015;102(3):639–47.
[125] van der Zwaluw NL, Dhonukshe-Rutten RA, van Wijngaarden JP, Brouwer-Brolsma EM, van de Rest O, In 't Veld PH, et al. Results of 2-year vitamin B treatment on cognitive performance: secondary data from an RCT. Neurology. 2014;83(23):2158–66.
[126] Dysken MW, Sano M, Asthana S, Vertrees JE, Pallaki M, Llorente M, et al. Effect of vitamin E and memantine on functional decline in Alzheimer disease: the TEAM-AD VA cooperative randomized trial. JAMA. 2014;311 (1):33–44.
[127] Aisen PS, Schneider LS, Sano M, Diaz-Arrastia R, van Dyck CH, Weiner MF, et al. High-dose B vitamin supplementation and cognitive decline in Alzheimer disease: a randomized controlled trial. JAMA. 2008;300 (15):1774–83.
[128] Ascherio A, Weisskopf MG, O'Reilly E J, Jacobs EJ, McCullough ML, Calle EE, et al. Vitamin E intake and risk of amyotrophic lateral sclerosis. Ann Neurol. 2005;57(1):104–10.
[129] Dong R, Yang Q, Zhang Y, Li J, Zhang L, Zhao H. Meta-analysis of vitamin C, vitamin E and beta-carotene levels in the plasma of Alzheimer's disease patients]. Wei Sheng Yan Jiu. 2018;47(4):648–54.
[130] Lloret A, Badia MC, Mora NJ, Pallardo FV, Alonso MD, Vina J. Vitamin E paradox in Alzheimer's disease: it does not prevent loss of cognition and may even be detrimental. J Alzheimers Dis. 2009;17(1):143–9.
[131] Charlton KE, Rabinowitz TL, Geffen LN, Dhansay MA. Lowered plasma vitamin C, but not vitamin E, concentrations in dementia patients. J Nutr Health Aging. 2004;8(2):99–107.
[132] Chandra RK. Effect of vitamin and trace-element supplementation on cognitive function in elderly subjects. Nutrition. 2001;17(9):709–12.
[133] Carlson JJ, Farquhar JW, DiNucci E, Ausserer L, Zehnder J, Miller D, et al. Safety and efficacy of a ginkgo biloba-containing dietary supplement on cognitive function, quality of life, and platelet function in healthy, cognitively intact older adults. J Am Diet Assoc. 2007;107(3):422–32.
[134] Shim JS, Oh K, Kim HC. Dietary assessment methods in epidemiologic studies. Epidemiol Health. 2014;36: e2014009.
[135] Pasinetti GM, Eberstein JA. Metabolic syndrome and the role of dietary lifestyles in Alzheimer's disease. J Neurochem. 2008;106(4):1503–14.
[136] Trichopoulou A, Costacou T, Bamia C, Trichopoulos D. Adherence to a Mediterranean diet and survival in a Greek population. N Engl J Med. 2003;348 (26):2599–608.
[137] van Himbergen TM, Beiser AS, Ai M, Seshadri S, Otokozawa S, Au R, et al. Biomarkers for insulin resistance and inflammation and the risk for all-cause dementia and Alzheimer disease: results from the Framingham Heart study. Arch Neurol. 2012;69 (5):594–600.
[138] Wu L, Sun D. Adherence to Mediterranean diet and risk of developing cognitive disorders: an updated systematic review and meta-analysis of prospective cohort studies. Sci Rep. 2017;7:41317.
[139] Singh B, Parsaik AK, Mielke MM, Erwin PJ, Knopman DS, Petersen RC, et al. Association of Mediterranean diet with mild cognitive impairment and Alzheimer's disease: a systematic review and meta-analysis. J Alzheimers Dis. 2014;39(2):271–82.
[140] Hanson LC, Ersek M, Lin FC, Carey, TS. Outcomes of feeding problems in advanced dementia in a nursing home population. J Am Geriatr Soc. 2013;61:1692–7.
[141] Ticinesi A, Nouvenne A, Lauretani F, Prati B, Cerundolo N, Maggio M, et al. Survival in older adults with dementia and eating problems: to PEG or not to PEG? Clin Nutr. 2016;35(6):1512–6.
[142] Ma K, Xiong N, Shen Y, Han C, Liu L, Zhang G, et al. Weight loss and malnutrition in patients with Parkinson's disease: current Knowledge and future Prospects. Front Aging Neurosci. 2018;10:1.

[143] Lorefalt B, Ganowiak W, Palhagen S, Toss G, Unosson M, Granerus AK. Factors of importance for weight loss in elderly patients with Parkinson's disease. Acta Neurol Scand. 2004;110(3):180–7.
[144] Kim HJ, Oh ES, Lee JH, Moon JS, Oh JE, Shin JW, et al. Relationship between changes of body mass index (BMI) and cognitive decline in Parkinson's disease (PD). Arch Gerontol Geriatr. 2012;55(1):70–2.
[145] Gibas KJ. The starving brain: overfed meets undernourished in the pathology of mild cognitive impairment (MCI) and Alzheimer's disease (AD). Neurochem Int. 2017;110:57–68.
[146] Cova I, Clerici F, Maggiore L, Pomati S, Cucumo V, Ghiretti R, et al. Body mass index Predicts progression of mild cognitive impairment to dementia. Dement Geriatr Cogn Disord. 2016;41(3-4):172–80.
[147] Faxen-Irving G, Basun H, Cederholm T. Nutritional and cognitive relationships and long-term mortality in patients with various dementia disorders. Age Ageing. 2005;34(2):136–41.
[148] Joo SH, Yun SH, Kang DW, Hahn CT, Lim HK, Lee CU. Body mass index in mild cognitive impairment According to Age, Sex, cognitive intervention, and hypertension and risk of progression to Alzheimer's disease. Front Psychiatry. 2018;9:142.
[149] Profenno LA, Porsteinsson AP, Faraone SV. Meta-analysis of Alzheimer's disease risk with obesity, diabetes, and related disorders. Biol Psychiatry. 2010;67 (6):505–12.
[150] Benstead T, Jackson-Tarlton C, Leddin D. Nutrition with gastrostomy feeding tubes for amyotrophic lateral sclerosis in Canada. Can J Neurol Sci. 2016;43(6):796–800.
[151] Park Y, Park J, Kim Y, Baek H, Kim SH. Association between nutritional status and disease severity using the amyotrophic lateral sclerosis (ALS) functional rating scale in ALS patients. Nutrition. 2015;31(11-12):1362–7.
[152] Mauriz E, Laliena A, Vallejo D, Tunon MJ, Rodriguez-Lopez JM, Rodriguez-Perez R, et al. Effects of a low-fat diet with antioxidant supplementation on biochemical markers of multiple sclerosis long-term care residents. Nutr Hosp. 2013;28 (6):2229–35.
[153] Burckhardt M, Herke M, Wustmann T, Watzke S, Langer G, Fink A. Omega-3 fatty acids for the treatment of dementia. Cochrane Database Syst Rev. 2016;4: CD009002.
[154] Knaze V, Rothwell JA, Zamora-Ros R, Moskal A, Kyro C, Jakszyn P, et al. A new food-composition database for 437 polyphenols in 19,899 raw and prepared foods used to estimate polyphenol intakes in adults from 10 European countries. Am J Clin Nutr. 2018.
[155] Strathearn KE, Yousef GG, Grace MH, Roy SL, Tambe MA, Ferruzzi MG, et al. Neuroprotective effects of anthocyanin- and proanthocyanidin-rich extracts in cellular models of Parkinsons disease. Brain Res. 2014;1555:60–77.
[156] Granzotto A, Zatta P. Resveratrol and Alzheimer's disease: message in a bottle on red wine and cognition. Front Aging Neurosci. 2014;6:95.
[157] Bastianetto S, Menard C, Quirion R. Neuroprotective action of resveratrol. Biochim Biophys Acta. 2015;1852(6):1195–201.
[158] Braidy N, Jugder BE, Poljak A, Jayasena T, Mansour H, Nabavi SM, et al. Resveratrol as a potential therapeutic candidate for the treatment and management of Alzheimer's disease. Curr Top Med Chem. 2016;16 (17):1951–60.
[159] Xu W, Wang H, Wan Y, Tan C, Li J, Tan L, et al. Alcohol consumption and dementia risk: a dose-response meta-analysis of prospective studies. Eur J Epidemiol. 2017;32(1):31–42.
[160] Jia Y, Wang N, Liu X. Resveratrol and amyloid-Beta: mechanistic insights. Nutrients. 2017;9(10.
[161] Freyssin A, Page G, Fauconneau B, Rioux Bilan A. Natural polyphenols effects on protein aggregates in Alzheimer's and Parkinson's prion-like diseases. Neural Regen Res. 2018;13(6):955–61.
[162] Witte AV, Kerti L, Margulies DS, Floel A. Effects of resveratrol on memory performance, hippocampal functional connectivity, and glucose metabolism in healthy older adults. J Neurosci. 2014;34(23):7862–70.
[163] Lagouge M, Argmann C, Gerhart-Hines Z, Meziane H, Lerin C, Daussin F, et al. Resveratrol improves mitochondrial function and protects against metabolic disease by activating SIRT1 and PGC-1alpha. Cell. 2006;127(6):1109–22.
[164] Baur JA, Pearson KJ, Price NL, Jamieson HA, Lerin C, Kalra A, et al. Resveratrol improves health and survival of mice on a high-calorie diet. Nature. 2006;444 (7117):337–42.
[165] Tian Y, Ma J, Wang W, Zhang L, Xu J, Wang K, et al. Resveratrol supplement inhibited the NF-kappaB inflammation pathway through activating AMPKalpha-SIRT1 pathway in mice with fatty liver. Mol Cell Biochem. 2016;422(1-2):75–84.
[166] Chung S, Yao H, Caito S, Hwang JW, Arunachalam G, Rahman I. Regulation of SIRT1 in cellular functions: role of polyphenols. Arch Biochem Biophys. 2010;501 (1):79–90.
[167] Donmez G, Wang D, Cohen DE, Guarente L. Sirt1 suppresses beta-amyloid production by activating the alpha-secretase gene ADAM10. Cell. 2010;142(2):320–32.
[168] Wang G, Chen L, Pan X, Chen J, Wang L, Wang W, et al. The effect of resveratrol on beta amyloid-induced memory impairment involves inhibition of phosphodiesterase-4 related signaling. Oncotarget. 2016;7 (14):17380–92.
[169] Zhao H, Wang Q, Cheng X, Li X, Li N, Liu T, et al. Inhibitive effect of resveratrol on the inflammation in cultured astrocytes and microglia induced by Abeta1-42. Neuroscience. 2018;379:390–404.
[170] Granzotto A, Zatta P. Resveratrol acts not through anti-aggregative pathways but mainly via its scavenging properties against Abeta and Abeta-metal complexes toxicity. PLoS One. 2011;6(6):e21565.
[171] Hubbard BP, Sinclair DA. Small molecule SIRT1 activators for the treatment of aging and age-related diseases. Trends Pharmacol Sci. 2014;35(3):146–54.
[172] Abuznait AH, Qosa H, Busnena BA, El Sayed KA, Kaddoumi A. Olive-oil-derived oleocanthal enhances beta-amyloid clearance as a potential neuroprotective

mechanism against Alzheimer's disease: in vitro and in vivo studies. ACS Chem Neurosci. 2013;4(6):973–82.
[173] Dong S, Huang X, Zhen J, Van Halm-Lutterodt N, Wang J, Zhou C, et al. Dietary vitamin E status Dictates oxidative stress outcomes by modulating effects of fish Oil supplementation in Alzheimer disease model APPswe/PS1dE9 mice. Mol Neurobiol. 2018;55 (12):9204–19.
[174] Beauchamp GK, Keast RS, Morel D, Lin J, Pika J, Han Q, et al. Phytochemistry: ibuprofen-like activity in extra-virgin olive oil. Nature. 2005;437(7055):45–6.
[175] Qosa H, Mohamed LA, Batarseh YS, Alqahtani S, Ibrahim B, LeVine H, et al. Extra-virgin olive oil attenuates amyloid-beta and tau pathologies in the brains of TgSwDI mice. J Nutr Biochem. 2015;26(12):1479–90.
[176] Rigacci S, Stefani M. Nutraceutical properties of olive oil polyphenols. An itinerary from cultured cells through animal models to humans. Int J Mol Sci. 2016;17(6): pii: E843.
[177] Pang KL, Chin KY. The biological Activities of oleocanthal from a molecular perspective. Nutrients. 2018;20 (11):4037–50.
[178] Hosseini B, Berthon BS, Saedisomeolia A, Starkey MR, Collison A, Wark PAB, et al. Effects of fruit and vegetable consumption on inflammatory biomarkers and immune cell populations: a systematic literature review and meta-analysis. Am J Clin Nutr. 2018.
[179] Kang JH, Ascherio A, Grodstein F. Fruit and vegetable consumption and cognitive decline in aging women. Ann Neurol. 2005;57(5):713–20.
[180] Okamoto K, Kihira T, Kobashi G, Washio M, Sasaki S, Yokoyama T, et al. Fruit and vegetable intake and risk of amyotrophic lateral sclerosis in Japan. Neuroepidemiology. 2009;32(4):251–6.
[181] Staubo SC, Aakre JA, Vemuri P, Syrjanen JA, Mielke MM, Geda YE, et al. Mediterranean diet, micronutrients and macronutrients, and MRI measures of cortical thickness. Alzheimers Dement. 2017;13(2):168–77.
[182] Taylor MK, Sullivan DK, Swerdlow RH, Vidoni ED, Morris JK, Mahnken JD, et al. A high-glycemic diet is associated with cerebral amyloid burden in cognitively normal older adults. Am J Clin Nutr. 2017;106 (6):1463–70.
[183] Ruhlmann C, Wolk T, Blumel T, Stahn L, Vollmar B, Kuhla A. Long-term caloric restriction in ApoE-deficient mice results in neuroprotection via Fgf21-induced AMPK/mTOR pathway. Aging (Albany NY. 2016;8(11):2777–89.
[184] Schafer MJ, Alldred MJ, Lee SH, Calhoun ME, Petkova E, Mathews PM, et al. Reduction of beta-amyloid and gamma-secretase by calorie restriction in female Tg2576 mice. Neurobiol Aging. 2015;36(3):1293–302.
[185] Hadad N, Unnikrishnan A, Jackson JA, Masser DR, Otalora L, Stanford DR, et al. Caloric restriction mitigates age-associated hippocampal differential CG and non-CG methylation. Neurobiol Aging. 2018;67:53–66.
[186] Brownlow ML, Joly-Amado A, Azam S, Elza M, Selenica ML, Pappas C, et al. Partial rescue of memory deficits induced by calorie restriction in a mouse model of tau deposition. Behav Brain Res. 2014;271:79–88.
[187] Joris PJ, Plat J, Kusters YH, Houben AJ, Stehouwer CD, Schalkwijk CG, et al. Diet-induced weight loss improves not only cardiometabolic risk markers but also markers of vascular function: a randomized controlled trial in abdominally obese men. Am J Clin Nutr. 2017;105 (1):23–31.
[188] Wycherley TP, Brinkworth GD, Keogh JB, Noakes M, Buckley JD, Clifton PM. Long-term effects of weight loss with a very low carbohydrate and low fat diet on vascular function in overweight and obese patients. J Intern Med. 2010;267(5):452–61.
[189] Chapman CD, Schioth HB, Grillo CA, Benedict C. Intranasal insulin in Alzheimer's disease: food for thought. Neuropharmacology. 2018;136(Pt B): 196–201.
[190] de Nazareth AM. Type 2 diabetes mellitus in the pathophysiology of Alzheimer's disease. Dement Neuropsychol. 2017;11(2):105–13.
[191] Kleinridders A, Ferris HA, Cai W, Kahn CR. Insulin action in brain regulates systemic metabolism and brain function. Diabetes. 2014;63(7):2232–43.
[192] Wijesekara N, Goncalves RA, De Felice FG, Fraser PE. Impaired peripheral glucose homeostasis and Alzheimer's disease. Neuropharmacology. 2018;136(Pt B):172–181.
[193] Wei X, Gao H, Zou J, Liu X, Chen D, Liao J, et al. Contra-directional Coupling of Nur77 and Nurr1 in neurodegeneration: a novel mechanism for Memantine-induced anti-inflammation and anti-mitochondrial impairment. Mol Neurobiol. 2016;53 (9):5876–92.
[194] Wang R, Chen Z, Fu Y, Wei X, Liao J, Liu X, et al. Plasma cystatin C and high-density lipoprotein Are important biomarkers of Alzheimer's disease and vascular dementia: a cross-sectional study. Front Aging Neurosci. 2017;9(26).
[195] Ingram DK, Zhu M, Mamczarz J, Zou S, Lane MA, Roth GS, et al. Calorie restriction mimetics: an emerging research field. Aging Cell. 2006;5(2):97–108.
[196] Mattson MP. Gene-diet interactions in brain aging and neurodegenerative disorders. Ann Intern Med. 2003;139(5 Pt 2):441–4.
[197] Arnold SE, Arvanitakis Z, Macauley-Rambach SL, Koenig AM, Wang HY, Ahima RS, et al. Brain insulin resistance in type 2 diabetes and Alzheimer disease: concepts and conundrums. Nat Rev Neurol. 2018;14 (3):168–81.
[198] Willette AA, Johnson SC, Birdsill AC, Sager MA, Christian B, Baker LD, et al. Insulin resistance predicts brain amyloid deposition in late middle-aged adults. Alzheimers Dement. 2015;11(5):504–10 e1.
[199] Zhang Y, Huang NQ, Yan F, Jin H, Zhou SY, Shi JS, et al. Diabetes mellitus and Alzheimer's disease: GSK-3beta as a potential link. Behav Brain Res. 2018;339:57–65.
[200] An Y, Varma VR, Varma S, Casanova R, Dammer E, Pletnikova O, et al. Evidence for brain glucose dysregulation in Alzheimer's disease. Alzheimers Dement. 2018;14(3):318–29.
[201] Sims-Robinson C, Kim B, Rosko A, Feldman EL. How does diabetes accelerate Alzheimer disease pathology? Nat Rev Neurol. 2010;6(10):551–9.

[202] Wood H. Alzheimer disease: Is p-tau the missing link between insulin resistance and AD? Nat Rev Neurol. 2017;13(12):706.
[203] Rodriguez-Rodriguez P, Sandebring-Matton A, Merino-Serrais P, Parrado-Fernandez C, Rabano A, Winblad B, et al. Tau hyperphosphorylation induces oligomeric insulin accumulation and insulin resistance in neurons. Brain. 2017;140(12):3269–85.
[204] Gomez G, Beason-Held LL, Bilgel M, An Y, Wong DF, Studenski S, et al. Metabolic syndrome and amyloid accumulation in the aging brain. J Alzheimers Dis. 2018;65(2):629–39.
[205] Najem D, Bamji-Mirza M, Chang N, Liu QY, Zhang W. Insulin resistance, neuroinflammation, and Alzheimer's disease. Rev Neurosci. 2014;25(4):509–25.
[206] Hiltunen M, Khandelwal VK, Yaluri N, Tiilikainen T, Tusa M, Koivisto H, et al. Contribution of genetic and dietary insulin resistance to Alzheimer phenotype in APP/PS1 transgenic mice. J Cell Mol Med. 2012;16 (6):1206–22.
[207] Ma L, Dong W, Wang R, Li Y, Xu B, Zhang J, et al. Effect of caloric restriction on the SIRT1/mTOR signaling pathways in senile mice. Brain Res Bull. 2015;116:67–72.
[208] Yang L, Wang H, Liu L, Xie A. The role of insulin/IGF-1/PI3K/Akt/GSK3beta signaling in Parkinson's disease dementia. Front Neurosci. 2018;12:73.
[209] Matsuda S, Nakagawa Y, Tsuji A, Kitagishi Y, Nakanishi A, Murai T. Implications of PI3K/AKT/PTEN signaling on superoxide dismutases expression and in the pathogenesis of Alzheimer's disease. Diseases. 2018;6(2).
[210] Perera ND, Turner BJ. Ampk signalling and defective energy metabolism in amyotrophic lateral sclerosis. Neurochem Res. 2016;41(3):544–53.
[211] Vining EP, Freeman JM, Ballaban-Gil K, Camfield CS, Camfield PR, Holmes GL, et al. A multicenter study of the efficacy of the ketogenic diet. Arch Neurol. 1998;55(11):1433–7.
[212] Westman EC, Feinman RD, Mavropoulos JC, Vernon MC, Volek JS, Wortman JA, et al. Low-carbohydrate nutrition and metabolism. Am J Clin Nutr. 2007;86 (2):276–84.
[213] Cassady BA, Charboneau NL, Brys EE, Crouse KA, Beitz DC, Wilson T. Effects of low carbohydrate diets high in red meats or poultry, fish and shellfish on plasma lipids and weight loss. Nutr Metab (Lond. 2007;4:23.
[214] Villaluz MM, Lomax LB, Jadhav T, Cross JH, Scheffer IE. The ketogenic diet is effective for refractory epilepsy associated with acquired structural epileptic encephalopathy. Dev Med Child Neurol. 2018;60 (7):718–23.
[215] McDonald TJW, Cervenka MC. Ketogenic diets for adults with highly refractory epilepsy. Epilepsy Curr. 2017;17(6):346–50.
[216] Veyrat-Durebex C, Reynier P, Procaccio V, Hergesheimer R, Corcia P, Andres CR, et al. How can a ketogenic diet improve motor function? Front Mol Neurosci. 2018;11:15.
[217] Taylor MK, Sullivan DK, Mahnken JD, Burns JM, Swerdlow RH. Feasibility and efficacy data from a ketogenic diet intervention in Alzheimer's disease. Alzheimers Dement (N Y). 2018;4:28–36.
[218] Boison D. New insights into the mechanisms of the ketogenic diet. Curr Opin Neurol. 2017;30(2):187–92.
[219] Sada N, Inoue T. Electrical control in neurons by the ketogenic diet. Front Cell Neurosci. 2018;12:208.
[220] Maalouf M, Rho JM, Mattson MP. The neuroprotective properties of calorie restriction, the ketogenic diet, and ketone bodies. Brain Res Rev. 2009;59 (2):293–315.
[221] Henderson ST, Vogel JL, Barr LJ, Garvin F, Jones JJ, Costantini LC. Study of the ketogenic agent AC-1202 in mild to moderate Alzheimer's disease: a randomized, double-blind, placebo-controlled, multicenter trial. Nutr Metab (Lond). 2009;6:31.
[222] Krikorian R, Shidler MD, Dangelo K, Couch SC, Benoit SC, Clegg DJ. Dietary ketosis enhances memory in mild cognitive impairment. Neurobiol Aging. 2012;33(2):425 e19–27.
[223] Noh HS, Hah YS, Nilufar R, Han J, Bong JH, Kang SS, et al. Acetoacetate protects neuronal cells from oxidative glutamate toxicity. J Neurosci Res. 2006;83 (4):702–9.
[224] Kashiwaya Y, Takeshima T, Mori N, Nakashima K, Clarke K, Veech RL. D-beta-hydroxybutyrate protects neurons in models of Alzheimer's and Parkinson's disease. Proc Natl Acad Sci U S A. 2000;97(10):5440–4.
[225] Puchowicz MA, Emancipator DS, Xu K, Magness DL, Ndubuizu OI, Lust WD, et al. Adaptation to chronic hypoxia during diet-induced ketosis. Adv Exp Med Biol. 2005;566:51–7.
[226] Wang BH, Hou Q, Lu YQ, Jia MM, Qiu T, Wang XH, et al. Ketogenic diet attenuates neuronal injury via autophagy and mitochondrial pathways in pentylenetetrazol-kindled seizures. Brain Res. 2018;1678:106–15.
[227] Augustin K, Khabbush A, Williams S, Eaton S, Orford M, Cross JH, et al. Mechanisms of action for the medium-chain triglyceride ketogenic diet in neurological and metabolic disorders. Lancet Neurol. 2018;17(1):84–93.
[228] Tsai SF, Wu HT, Chen PC, Chen YW, Yu M, Wang TF, et al. High-fat diet suppresses the astrocytic process arborization and downregulates the glial glutamate transporters in the hippocampus of mice. Brain Res. 2018;1700:66–77.
[229] Ferreiro A, Crook N, Gasparrini AJ, Dantas G. Multiscale evolutionary dynamics of host-associated microbiomes. Cell. 2018;172(6):1216–27.
[230] Sharon G, Sampson TR, Geschwind DH, Mazmanian SK. The central nervous system and the gut microbiome. Cell. 2016;167(4):915–32.
[231] Petra AI, Panagiotidou S, Hatziagelaki E, Stewart JM, Conti P, Theoharides TC. Gut-Microbiota-Brain axis and Its effect on neuropsychiatric disorders with suspected immune dysregulation. Clin Ther. 2015;37 (5):984–95.
[232] Grasset E, Puel A, Charpentier J, Collet X, Christensen JE, Terce F, et al. A specific Gut microbiota dysbiosis of type 2 diabetic mice induces GLP-1 resistance through an enteric NO-dependent and gut-brain axis mechanism. Cell Metab. 2017;26(1):278.
[233] Wu SC, Cao ZS, Chang KM, Juang JL. Intestinal microbial dysbiosis aggravates the progression of

Alzheimer's disease in Drosophila. Nat Commun. 2017;8(1):24.
[234] Lai SW, Liao KF, Lin CL, Sung FC. Irritable bowel syndrome correlates with increased risk of Parkinson's disease in Taiwan. Eur J Epidemiol. 2014;29(1):57–62.
[235] Belkaid Y, Hand TW. Role of the microbiota in immunity and inflammation. Cell. 2014;157(1):121–41.
[236] Pistollato F, Sumalla Cano S, Elio I, Masias Vergara M, Giampieri F, Battino M. Role of gut microbiota and nutrients in amyloid formation and pathogenesis of Alzheimer disease. Nutr Rev. 2016;74(10):624–34.
[237] Sampson TR, Debelius JW, Thron T, Janssen S, Shastri GG, Ilhan ZE, et al. Gut microbiota regulate motor deficits and neuroinflammation in a model of Parkinson's disease. Cell. 2016;167(6):1469–80 e12.
[238] Vogt NM, Romano KA, Darst BF, Engelman CD, Johnson SC, Carlsson CM, et al. The gut microbiota-derived metabolite trimethylamine N-oxide is elevated in Alzheimer's disease. Alzheimers Res Ther. 2018;10(1):124.
[239] Mestre L, Carrillo-Salinas FJ, Mecha M, Feliu A, Espejo C, Alvarez-Cermeno JC, et al. Manipulation of gut microbiota influences immune responses, axon preservation, and motor disability in a model of progressive multiple sclerosis. Front Immunol. 2019;10:1374.
[240] Tsai GE, Falk WE, Gunther J, Coyle JT. Improved cognition in Alzheimer's disease with short-term D-cycloserine treatment. Am J Psychiatry. 1999;156(3):467–9.
[241] Molloy DW, Standish TI, Zhou Q, Guyatt G, Group DS. A multicenter, blinded, randomized, factorial controlled trial of doxycycline and rifampin for treatment of Alzheimer's disease: the DARAD trial. Int J Geriatr Psychiatry. 2013;28(5):463–70.
[242] Bonfili L, Cecarini V, Cuccioloni M, Angeletti M, Berardi S, Scarpona S, et al. Slab51 probiotic formulation activates SIRT1 pathway promoting antioxidant and neuroprotective effects in an AD mouse model. Mol Neurobiol. 2018;55(10):7987–8000.
[243] Minter MR, Zhang C, Leone V, Ringus DL, Zhang X, Oyler-Castrillo P, et al. Antibiotic-induced perturbations in gut microbial diversity influences neuroinflammation and amyloidosis in a murine model of Alzheimer's disease. Sci Rep. 2016;6:30028.
[244] Brandscheid C, Schuck F, Reinhardt S, Schafer KH, Pietrzik CU, Grimm M, et al. Altered gut microbiome composition and tryptic activity of the 5xFAD Alzheimer's mouse model. J Alzheimers Dis. 2017;56(2):775–88.
[245] Unger MM, Spiegel J, Dillmann KU, Grundmann D, Philippeit H, Burmann J, et al. Short chain fatty acids and gut microbiota differ between patients with Parkinson's disease and age-matched controls. Parkinsonism Relat Disord. 2016;32:66–72.
[246] Yamada T, Shimizu K, Ogura H, Asahara T, Nomoto K, Yamakawa K, et al. Rapid and sustained long-term decrease of fecal short-chain fatty acids in critically Ill patients with systemic inflammatory response syndrome. JPEN J Parenter Enteral Nutr. 2015;39(5):569–77.
[247] Louveau A, Smirnov I, Keyes TJ, Eccles JD, Rouhani SJ, Peske JD, et al. Structural and functional features of central nervous system lymphatic vessels. Nature. 2015;523(7560):337–41.
[248] Goehler LE, Gaykema RP, Opitz N, Reddaway R, Badr N, Lyte M. Activation in vagal afferents and central autonomic pathways: early responses to intestinal infection with Campylobacter jejuni. Brain Behav Immun. 2005;19(4):334–44.
[249] Bravo JA, Forsythe P, Chew MV, Escaravage E, Savignac HM, Dinan TG, et al. Ingestion of Lactobacillus strain regulates emotional behavior and central GABA receptor expression in a mouse via the vagus nerve. Proc Natl Acad Sci U S A. 2011;108(38):16050–5.
[250] Hill-Burns EM, Debelius JW, Morton JT, Wissemann WT, Lewis MR, Wallen ZD, et al. Parkinson's disease and Parkinson's disease medications have distinct signatures of the gut microbiome. Mov Disord. 2017;32(5):739–49.
[251] Haran JP, Bhattarai SK, Foley SE, Dutta P, Ward DV, Bucci V, et al. Alzheimer's disease microbiome is associated with dysregulation of the anti-inflammatory P-Glycoprotein pathway. MBio. 2019;10(3).
[252] Hopfner F, Kunstner A, Muller SH, Kunzel S, Zeuner KE, Margraf NG, et al. Gut microbiota in Parkinson disease in a northern German cohort. Brain Res. 2017;1667:41–5.
[253] Keshavarzian A, Green SJ, Engen PA, Voigt RM, Naqib A, Forsyth CB, et al. Colonic bacterial composition in Parkinson's disease. Mov Disord. 2015;30(10):1351–60.
[254] Shanahan F, van Sinderen D, O'Toole PW, Stanton C. Feeding the microbiota: transducer of nutrient signals for the host. Gut. 2017;66(9):1709–17.
[255] Claesson MJ, Jeffery IB, Conde S, Power SE, O'Connor EM, Cusack S, et al. Gut microbiota composition correlates with diet and health in the elderly. Nature. 2012;488(7410):178–84.
[256] Sonnenburg ED, Sonnenburg JL. Starving our microbial self: the deleterious consequences of a diet deficient in microbiota-accessible carbohydrates. Cell Metab. 2014;20(5):779–86.
[257] Wu GD, Chen J, Hoffmann C, Bittinger K, Chen YY, Keilbaugh SA, et al. Linking long-term dietary patterns with gut microbial enterotypes. Science. 2011;334(6052):105–8.
[258] Delzenne NM, Neyrinck AM, Cani PD. Modulation of the gut microbiota by nutrients with prebiotic properties: consequences for host health in the context of obesity and metabolic syndrome. Microb Cell Fact. 2011;10(Suppl 1):S10.
[259] Le Couteur DG, Solon-Biet S, Cogger VC, Mitchell SJ, Senior A, de Cabo R, et al. The impact of low-protein high-carbohydrate diets on aging and lifespan. Cell Mol Life Sci. 2016;73(6):1237–52.
[260] Guarente L, Picard F. Calorie restriction–the SIR2 connection. Cell. 2005;120(4):473–82.
[261] Solon-Biet SM, Mitchell SJ, de Cabo R, Raubenheimer D, Le Couteur DG, Simpson SJ. Macronutrients and caloric intake in health and longevity. J Endocrinol. 2015;226(1):R17–28.
[262] Simpson SJ, Le Couteur DG, Raubenheimer D. Putting the balance back in diet. Cell. 2015;161(1):18–23.
[263] Simpson SJ, Raubenheimer D. Obesity: the protein leverage hypothesis. Obes Rev. 2005;6(2):133–42.

[264] Calikoglu A, Karayal A, D'Ercole A. Nutritional regulation of IGF-I expression during brain development in mice. Pediatr Res. 2001;49(2):197–202.
[265] Trejo JL, Carro E, Torres-Aleman I. Circulating insulin-like growth factor I mediates exercise-induced increases in the number of new neurons in the adult hippocampus. J Neurosci. 2001;21 (5):1628–34.
[266] Mishra N, Lata S, Deshmukh P, Kamat K, Surolia A, Banerjee T. Insulin signaling pathway protects neuronal cell lines by Sirt3 mediated IRS2 activation. Biofactors. 2018;44(3):224–36.
[267] Lee J, Baek H, Kim SH, Park Y. Association between estimated total daily energy expenditure and stage of amyotrophic lateral sclerosis. Nutrition. 2017;33:181–6.