

Nutrition

Preservation of cognitive ability well into old age is essential to promote an adequate health status. Food and nutrition add an important dimension to improve health. The most practical outcome of any research in the relationship between diet and nutrition to ageing would be a better understanding of how nutrition related behaviours can help to maintain an optimal quality of life. Studies are also required to establish possible links between nutrient intake (i.e. nutritional status) and cognitive impairment, and whether it is possible to inhibit or delay the onset of dementia by dietary modifications.

Cognitive impairment has in most cases a multifactorial origin. As far as nutrition is concerned, it can be concluded that Alzheimer's and Vascular Dementia partly share the same risk factors, which is consistent with the current opinion about a link existing between these two types of dementia (1). Nutrition-related risk factors may include inadequacy of essential nutrients (vitamins B12, B6, folic acid and antioxidants C, E and β -carotene) and nutrition-related disorders, as high cholesterol, high carb. diets, saturated and trans fats, elevated triglyceride levels, high blood pressure, and diabetes. Some of the risk factors can be present over a long time before cognitive impairment becomes evident. Severe or even moderate malnutrition may cause an enhanced risk of dementia and Alzheimer's in susceptible people. However, even optimal intake of nutrients does not protect people from dementia.

The typical 'Mediterranean' diet, which includes a high consumption of olive oil and fish and therefore elevated intakes of monounsaturated fatty acids and omega-3 polyunsaturated fatty acids, seems to be protective against age-related cognitive decline (2). This outcome can be due in part to the antioxidant and anti-inflammatory compounds in olive oil (rich in phenols tocopherols and polyphenols), and in part to the role of fatty acids in maintaining the structural integrity of neuronal membranes. Advancing age has been shown to be associated with an increase in monounsaturated fatty acid content together with a decrease in polyunsaturated fatty acid content within neuronal membranes (3).

It is not yet clear whether increasing consumption of antioxidants in the diet will help to prevent or delay cognitive impairment. However, standard dietary recommendations for healthier lifestyles (e.g. eating more fruit and vegetables) may have the added potential benefits of increasing antioxidant intake and helping to protect cognitive function. On the other hand, we should bear in mind that incipient dementia may also change dietary habits, that is, malnutrition can be a consequence of rather than a cause of cognitive impairment.

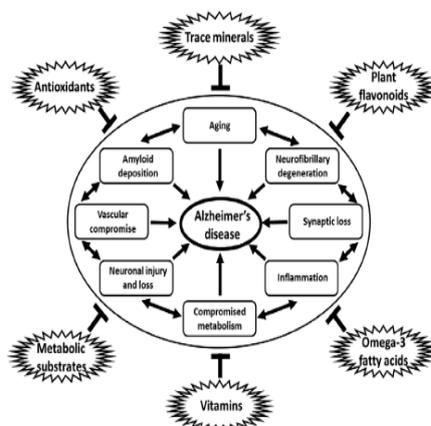


Diagram of multiple influences of dietary constituents on cellular pathways and process linked to neurodegeneration in Alzheimer's. Antioxidants, trace minerals, flavonoids (found in fruit and vegetables), metabolic substrates and modulators (energy sources), vitamins, and omega-3 fatty acids, among others, have all been shown to down regulate the many pathological processes linked to the development of Alzheimer's, including aging, amyloid deposition, neurofibrillary degeneration, synapse loss, inflammation, metabolic compromise, loss of vascular integrity (blood flow etc), and neuronal injury and loss. Note: specific dietary factors may have more than one potential mechanism of action on the pathogenic processes contributing to neurodegeneration in Alzheimer's. Links between pathological processes implicated in the development of Alzheimer's may not be linear, but rather additive and are shown in a circular fashion without implication for specific linkages or temporal associations between such processes.

Whilst the search for a cure for dementia remains elusive, there is much hope that preventative strategies, such as dietary modification and nutritional supplementation, may reduce the global

burden of Alzheimer's. A nutritional approach to prevent, slow, or halt the progression of disease is a promising strategy that has been widely investigated. A lot of research suggests that nutritional intake may influence the development and progression of Alzheimer's. Many nutritional supplements and dietary modifications may directly influence the causal contributions of increased oxidative stress, defects in mitochondrial disorders and cellular energy production, chronic inflammatory mechanisms, and even direct pathways to amyloid accumulation and neurofibrillary degeneration that contribute to the degenerative cascade in Alzheimer's, see above Figure. Nutritional modifications have the advantage of being cost effective, easy to implement, socially acceptable and generally safe and devoid of significant adverse events in most cases. Many nutritional interventions have been studied and continue to be evaluated in hopes of finding a successful compound that can be used for the prevention and or treatment of Alzheimer's (4). A discussion of the full complexity of dietary and nutritional interventions for the prevention of Alzheimer's could fill a large book but for the moment consider three fundamentally important considerations in interpreting the available data on nutritional supplementation for the prevention of Alzheimer's eg.,

- (a) Despite our understanding that regulation of metabolic processes are complex and may require multiple nutritional influences to correct the aberrant processes leading to Alzheimer's, traditional experimental design and study to date has largely focused on the use of single agents. Studies of combination therapies may be extremely important for the identification of truly effective nutritional strategies;
- (b) Considerations of dietary excess and the negative consequences of some dietary constituents (especially those characterizing the current "Western" diet, may interfere with the potentially positive effects of specific nutritional interventions). This has been clearly shown in regards to benefits of omega-3 fatty acids that are neutralized by high dietary intake of omega-6 and saturated fats;
- (c) Our current understanding of Alzheimer's includes a preclinical phase ranging from 10 to 20 years in which preventative strategies may need to be maintained in order to see their effects. At best, available prevention data is derived from trials with short intervention periods, with few studies extending to a 3 year period(4).

Yet it is possible, despite the wealth of retrospective and prospective data available that nutritional interventions for the prevention of Alzheimer's may be effective, it is equally possible that they may serve to only supplement direct disease modifying treatment, and in themselves are ineffective at modulating the Alzheimer's disease state as such. So it is possible that dietary modulation and nutritional supplementation serves only to bolster normal health mechanisms that are a natural deterrent of chronic health conditions such as Alzheimer's without really possessing any discrete disease specificity. Future investigations in the area of nutritional and dietary prevention of Alzheimer's will have to consider these potential confounds and overcome them if nutritional and dietary supplementation and modification are ever to become part of the clinical care paradigm for the prevention and treatment of Alzheimer's.

In a systematic study of a number of databases, it was found that higher adherence to Mediterranean diet was associated with better cognitive function, lower rates of cognitive decline, and reduced risk of Alzheimer disease. Further controlled trials promoting a Mediterranean diet would help establish whether improved adherence helps to prevent or delay the onset of Alzheimer disease and dementia (5). The Mediterranean diet has been associated with reduced risk for a wide range of age-related conditions such as stroke, type 2 diabetes and cardiovascular disease (6,7,8). The traditional Mediterranean diet refers to a multi-nutrient diet characterized by high intake of fruits, vegetables, cereals, and legumes; low consumption of saturated fats with olive oil as the main source of fat; moderate consumption of fish; low to moderate intake of dairy products (in the form

of yogurt and cheese); low consumption of red meat and meat products; and moderate amount of alcohol (especially wine) usually consumed during meals. A number of reviews have presented evidence for an association between a Mediterranean-type diet and slower cognitive decline. In the light of such findings, it is likely that improving adherence to the Mediterranean diet may delay or prevent the onset of dementia and Alzheimer's (9,10, 15). The benefits of Mediterranean diet adherence were particularly evident in studies with mean study starting ages above 75 years, possibly because the higher risk of incident cognitive problems in this age group made it easier to detect differences in outcomes between those who consumed a Mediterranean diet and those who did not (5). Evidence is accumulating for the effectiveness of the Mediterranean dietary pattern on the prevention of various age-related diseases, including dementia and that stricter adherence to Mediterranean diet is associated with slower cognitive decline and reduced risk of Alzheimer disease.

Potential underlying mechanisms in the Mediterranean diet may be a result of multiple biologic mechanisms. Relationships with reduced risk of coronary heart disease, hypertension, diabetes, high cholesterol, increased blood pressure, high blood sugar and excess body fat around the waist (11) have all been observed, and these conditions have also been associated with mild cognitive impairment, dementia, or Alzheimer disease. Higher adherence may also facilitate metabolic control because it has been related to improved insulin sensitivity (The pancreas is an organ that regulates blood sugar and secretes insulin in response to high blood sugar) and glucose metabolism. Furthermore, oxidative stress increases with age and results in oxidative damage (caused by free unstable molecules that damage or "oxidize" cells throughout the body) a state often observed in the brain of patients with Alzheimer disease (12). Typical components of the Mediterranean diet (namely fruits, vegetables, wine, and virgin olive oil) are rich in antioxidants such as vitamin C and E, carotenoids, and flavonoids hence decreased oxidative stress found in people adhering to a Mediterranean type diet could partially explain their lowered risk for dementia. Neurons are protected against oxidative stress by basic proteins such as the brain-derived neurotrophic factor (a family of biomolecules - nearly all of which are peptides or small proteins – that support the growth, survival, and differentiation of both developing and mature neurons) and there is some evidence that Mediterranean diet may increase plasma brain-derived neurotrophic factor concentrations. Neurotransmitter synthesis, synaptic plasticity, and cell metabolism are influenced by vitamin C and B complex vitamin intake (13). Inflammatory processes have also been suggested for Alzheimer's development. Higher concentrations of C-reactive protein, (produced in the liver, CRP is a blood test marker for inflammation in the body) have been associated with increased risk for cognitive decline, Alzheimer disease, and vascular dementia, whereas better adherence to Mediterranean diet has been associated with lower levels of C-reactive protein (14).

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