

EVIDENCE SUPPORTING NUTRITIONAL INTERVENTIONS FOR PERSONS IN EARLY STAGE AD

**EVIDENCE SUPPORTING NUTRITIONAL INTERVENTIONS FOR PERSONS  
IN EARLY STAGE ALZHEIMER'S DISEASE (AD)**

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**Abstract:** The purpose of this paper is to grade research evidence supporting nutritional interventions for persons with early stage dementias and to report the recommendations of a consensus panel. Thirty four studies were reviewed in the areas of dietary restriction, antioxidants, and Mediterranean diet with strong support from epidemiological studies found in all three areas. The body of evidence to support nutritional interventions in the prevention and treatment of AD is growing and has potential as a treatment modality following translational studies.

### Introduction

An extensive literature review and consensus paper was recently developed by the Dementia Day Camp (DDC) Research Group which pulls together the empirical evidence to support non-pharmacological approaches for management of early stage dementia. The full consensus paper describes research in the areas of exercise, cognitive stimulation, health promotion, multi-modal programs, and a category called "other interventions". This manuscript contains the literature review and evidence grading on nutritional interventions from the health promotion section. The purpose of this paper then, is to categorize and describe what is currently established in the realm of nutrition and early stage AD.

### Background

In 2001 there were 24 million people with dementia around the world. Looking at the aging of the population and specifically at people aged 60 and above, it was recently estimated that these figures would roughly double every 20 years, so there would be about 40 million people with dementia by 2020 and over 80 million by 2040. (1) Clinicians from all disciplines need to examine each and every type of intervention that may impact on the course of dementia since the current pharmacological treatments have limited effect over time and are not universally available.

The physiological mechanisms underlying neuronal damage in AD suggests that disease is caused by the same type of stress and environmental factors that cause aging in the rest of our bodies. Some people live to be over 90 years old and maintain normal cognitive functioning, while other people develop neurodegenerative diseases, such as AD, in their late 50's. The reason for the difference is extremely complex, involving the interaction of genetics and environment. Treatments for neurological diseases such as AD are focused on these two different aspects of brain aging. This review will focus on the

environmental aspect. The environment can be manipulated to promote positive brain aging, by introducing substances such as pharmaceuticals or nutrients to the brain to counteract negative effects of aging and promote neuronal integrity. Nutritional interventions, then, have the potential to affect neuronal integrity and possibly disease onset and progression.

### Search Method

The literature search took place between December 27, 2006 and January 16, 2007. Databases utilized in the search include PubMed, CINAHL, PsychInfo, and the Cochrane Database of Systematic Reviews. The following terms were used initially: dementia, health promotion, and Alzheimer's disease. Mesh terms were cross-referenced, such as dementia and health promotion to narrow the search. Once studies focusing on health promotion were identified, the search was narrowed to the identified topic. For example, dementia, Alzheimer's disease, and falls prevention were then cross-referenced for each database to fully search within each category. When a citation was found, links to related studies from a study to be included in the review were also explored. Further searches were done on the names of authors of research articles found in the initial search as well as on the names of their projects. Professionals working in the field contributed lists of references on early stage Alzheimer's disease interventions. Once articles were included in this review, further references were found using the ancestry method.

### Inclusion Criteria

All research articles addressing health promotion interventions (within the 5 identified categories) for persons in early-stage AD were included in the review. This review focuses on early stage AD, defined as having a diagnosis of early stage Alzheimer's disease with either an MMSE score of 18 or higher, a CDR score of 2.0 or less or a GDS of 2 or less.

Only research reports written in English were reviewed. Reports based on undocumented opinion were excluded.

### **Criteria for Grading the Strength and Consistency of Evidence**

This manuscript was developed from a systematic review and synthesis of current evidence. Research findings and other evidence, such as guidelines and standards from professional organizations, case reports and expert opinion were critiqued, analyzed and used as supporting evidence. The practice recommendations were assigned an evidence grade based upon the type and strength of evidence from research and other literature.

The grading schema used to make recommendations in this evidence-based review is:

A1= Evidence from well-designed meta-analysis or well-done systematic review with results that consistently support a specific action (e.g. assessment, intervention, or treatment)

A2= Evidence from one or more randomized controlled trials with consistent results

B1= Evidence from high quality evidence-based practice guideline

B2= Evidence from one or more quasi experimental studies with consistent results

C1= Evidence from observational studies with consistent results (e.g. correlational, descriptive studies)

C2= Inconsistent evidence from observational studies or controlled trials

D= Evidence from expert opinion, multiple case reports, or national consensus reports

### **Supporting Evidence**

The search produced only epidemiological studies testing nutritional interventions for persons in early-stage AD. Studies testing nutritional interventions for persons with AD included persons in the later disease stages and were conducted primarily in long-term care settings. Therefore, this review includes a sampling of eight research reports of nutritional interventions, mostly systematic reviews of the research literature, for prevention of neurodegeneration and preservation of neuronal function. The reviewed studies provide some support for nutritional practices that can be used as treatment modalities for AD. For clarity, the evidence is divided into three categories: 1) Dietary restriction, 2) Antioxidants, and 3) Mediterranean diet. Due to ethical considerations in testing some nutritional interventions, such as dietary restriction, many studies have used animal models, without benefit of translational research in human subjects.

#### ***Dietary restriction***

In a review of the literature, Mattson, Chan, and Duan (2002, evidence grade=A1) cite many studies that show a variety of effects of dietary restriction. (2) Animal studies show that

rodents fed a restricted diet compared with a control group of rodents who were allowed unlimited access to food revealed changes in gene expression in brain cells during aging and that dietary restriction can control those changes. Additional animal studies showed that dietary restriction has a positive impact at the neuronal level on prevention of neurodegeneration and also demonstrated a positive impact on actual neurodegeneration in the hippocampal and cortical areas, resulting in a positive effect on learning and memory.

Mattson, Duan, Chan, Cheng, Haughey, & Gary, et al. (2002, evidence grade=A1) conducted a review of 125 research articles on the cause, prevention, and treatment of neuronal damage in the brain and found that because two different areas of the brain contain neural stem cells capable of producing new neurons and glial cells, it is possible for the brain to repair itself after being damaged. (3) They also found evidence that the extent of neuronal death in early stage Alzheimer's disease may not be as great as initially thought and that neurons may instead be dysfunctional, but capable of revival. A variety of substances and strategies have been found to facilitate the protection and repair of neurons, including dietary restriction, ingestion of antioxidants, behavioral therapy.

Mattson (2000, Evidence grade = A2) observed that dietary restriction provides protection to neurons from oxidative stress by decreasing the amount of neurotoxic substances in the brain. (4) Further work indicated that dietary restriction actually increased the amount of newly generated neural cells in the adult brain, suggesting that this dietary manipulation can increase the brain's capacity for plasticity and repair. The data obtained from animal studies extrapolated to humans suggests that moderate levels of dietary restriction (1800-2200 calories/day) can dramatically reduce the incidence and severity of Alzheimer's disease, Parkinson's disease, and stroke.

Pasinetti and colleagues (2007, evidence grade=A1) conducted a review of the literature on AD and nutrition. (5) Based on their findings, the researchers conducted further studies using animals as subjects (mice) to determine the role of various nutritional strategies on AD. In these experimental studies, they found that high caloric intake based on saturated fat promotes AD type  $\beta$ -amyloidosis while dietary restriction based on reduced carbohydrate intake plays a preventive role in the onset of AD.

#### ***Antioxidants***

Research indicates that our cells become more vulnerable to oxidative stress as we age, which leaves us more vulnerable to the expression of neurodegenerative diseases such as AD. Further, epidemiological human and controlled animal and human studies are showing that introducing more antioxidants into our diets can reduce oxidative stress to our cells, thereby preventing and even reversing observable signs of neurodegeneration.

Joseph and colleagues (2000, Evidence grade=A2) reviewed animal and human studies of antioxidant effects on cellular vulnerability to oxidative stress. (6) The researchers concluded

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that antioxidants in both laboratory and in vitro experiments were effective in reducing oxidative stress on cells. Further, the team determined that ingestion of foods replete with antioxidants, such as blueberries, spinach, and strawberries, produced these same cellular protective effects and actually reversed signs of neurodegeneration in aged rodents.

Further support for the role of antioxidants as neural protectors at the cellular level was found in a large review of studies by Gonzalez-Gross, Marcos, and Pietrzik (2001, Evidence grade=A1). (7) The researchers called for further clinical studies to determine the link between nutrient intake/nutritional status with cognitive impairment and to determine if it is possible to inhibit or delay the onset of dementia using nutritional interventions.

Another review of almost 300 research articles (Esposito, Rotilo, DiMatteo, DiGiulio, Cacchio, & Algeri, 2002; Evidence grade=A1) confirmed the positive role antioxidants play in protecting neurons from damage by free radicals and reactive oxygen. (8) The researchers called for further research on the neuroprotective role of antioxidants in humans, especially using a combination of antioxidants.

In a review of over 100 studies on a variety of nutritional interventions in AD, Luchsinger and Mayeux (2004, Evidence grade=A1) determined there was insufficient evidence to permit specific recommendations on diet for the prevention and treatment of AD. (9) While in vitro studies show promise for a variety of diet modifications, very few human studies have been done to confirm those results. Also, contradictory findings require further clarification before dietary recommendations can be made.

A review of the literature by Martin (2004, Evidence grade=B2) demonstrates a relationship between dietary intake of foods containing antioxidants and reduced incidence of AD. [10] The review examined epidemiological studies of humans and in vitro animal studies.

An overview of the relationship between dementia and nutrition, which consisted of a literature review, (Salerno-Kennedy & Cashman, 2005, Evidence grade=A1) indicated that free radicals and oxidative stress play a role in neurodegenerative diseases and suggest that the consumption of antioxidants, particularly folate and vitamins B6 and B12, can be used to prevent AD. (11) The authors also recommend a diet with less saturated fat, and, based on the relationship between polyunsaturated fatty acid intake and lower risk for AD, greater consumption of fish and seafood.

Epidemiological studies support the relationship between reduced levels of vitamin B12 and high levels of the folate marker homocysteine and higher incidence of AD. Morris and colleagues (2005, Evidence grade B2) found a relationship between dietary intake of tocopherol (Vitamin E) with a reduced incidence of AD and other types of cognitive impairment in the 1993-2002 Chicago Health and Aging Project (n=1141 persons aged 65 or older). (12) A study of 321 men receiving services through the Boston Veterans Affairs

Medical Center concluded that intake of vitamins B6 and B12 and dietary folate all resulted in cognitive improvement, (Tucker, Qiao, Scott, Rosenberg, & Spiro, 2005; Evidence grade=B2). (13)

Another epidemiological study of 228 people being seen in a Swiss memory clinic compared levels of blood homocysteine, folate, and vitamin B12 in relation to incidence of dementia. Quadri and colleagues (2004, Evidence grade=B2) compared the blood levels of these three substances in persons who had no dementia (n=55), persons who had mild cognitive impairment with a CDR of .5 (n=81), and 92 persons with mild dementia and with a clinical diagnosis of AD (n=74) or vascular dementia (n=18). (14) Persons with the least amount of folate had significantly higher odds for mild cognitive impairment or dementia. In participants with a CDR of .5, the mean MMSE score was significantly lower in the group that had the highest levels of homocysteine than in the lowest group. The group concluded that folate deficiency may precede AD and vascular dementia.

In a longitudinal study, the Nun Study, the researchers examined predictors of AD incidence and severity (Snowdon, Tully, Smith, Riley, & Markesbery, 2000; Evidence grade=B2). (15) Findings related to nutritional intake demonstrated a strong association between low serum folate and atrophy of the cerebral cortex (N=30).

Ellinson, Thomas, and Patterson (2004, Evidence grade=A1) conducted a systematic review of published studies on the relationship between serum vitamin B12, folate, and total homocysteine and cognitive function in elderly persons. (16) A total of three case controlled studies were reviewed. Findings indicate that serum homocysteine was significantly higher in cases of cognitive impairment when compared with controls. However, there was a wide variation for both serum vitamin B12 and folate. In fact, one case study found a relationship between increased levels of vitamin B12 and decreased cognitive functioning scores. The authors conclude that no dietary recommendation for the prevention or treatment of Alzheimer's disease can be made in this area until further studies are done.

#### *Mediterranean Diet*

The diet of people who live in the Mediterranean area of Europe is rich in virgin olive oil, which is high in antioxidants. Other components of the Mediterranean diet are fish, red wine, and cereals. Epidemiological studies show that in countries where this diet was the norm, such as Spain, Greece, and Italy, there are lower incidence rates of cancer and cardiovascular disease. The high amounts of antioxidants in this diet are expected to play a neuroprotective role, thereby reducing the incidence of Alzheimer's disease as well.

A review of the literature completed by Solfrizzi, D'Introno, Colacicco, Capurso, Del Parigi, & Capurso et al. (2005, Evidence grade=A2) concluded that, based on lack of definitive evidence, no dietary recommendations on fish, vegetables, or

unsaturated fat can be made for the treatment of Alzheimer's disease because of the lack of clear clinical evidence that this type of diet is an effective treatment. (17) However this type of diet is still recommended for lowering the risk of cardiovascular disease, obesity, diabetes, and hypertension.

Another review of the literature by Panza Solfrizzi, Colacicco, D'Introno, Capurso, & Torres et al. (2004, Evidence grade=A1) provides support for the Mediterranean diet as protective against cognitive decline, when moderate amounts of olive oil, at least 100 g per day, are consumed as part of that diet. (18)

A study focusing on the chemicals found primarily in fish was conducted by Tully and colleagues (2003, Evidence grade=B2) to determine if there was a relationship between low serum cholesteryl ester-docosahexaenoic acid (DHA) levels and the severity of clinical dementia. (19) The 119 subjects had a mean MMSE score of 19.5. The control group (n=45) did not have dementia. They found serum cholesteryl ester-DHA levels were progressively reduced with the severity of dementia.

### Conclusions

Strong evidence supports that in both animals and humans reducing the number of calories ingested while maintaining adequate nutrition results in longer life and reduced risk for many different types of diseases, including AD. An emerging strategy for the prevention of AD and the treatment of early stage AD is to limit caloric intake without decreasing nutrition. However, one phenomenon associated with AD is weight loss, so this strategy needs further study before a recommendation can be made.

While many epidemiological studies have suggested that various nutrients can prevent or treat AD, there are few randomized controlled trials with humans as subjects. Before a definitive dietary recommendation can be made, translational research studies need to be conducted. The body of evidence to support nutritional interventions in the prevention and treatment of AD is growing and has potential as a treatment modality following translational studies.

### Recommendations from consensus group

Based on animal research and descriptive studies in humans, support for some dietary modifications can be found including fat and carbohydrate reduction and assuring adequate levels of Vitamin E, B6, and B12. The area of nutrition as an intervention for early AD is one that this workgroup believes will gain importance and promise in the future.

### Rating Summary

Topic of Study	% graded As "A"	% graded As "B"	% graded As "C"	% graded As "D"
Dietary restriction: n= 4	24%			
Antioxidants: n=11		29%		
Mediterranean diet: n=2	12%			
Total: n=17	71%	29%		

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