Protective measures that will decrease the incidence of Alzheimer's disease

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Dedication

In memory of my grandfather, A. Dale Shears (Papa).

To my mother, for being my inspiration, my best friend, and my greatest supporter.
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**Introduction**

As the United States population ages, the incidence and prevalence of dementia is becoming an increasing medical and social dilemma. Alzheimer’s disease (AD) is the most common pathology leading to dementia, affecting approximately 15 million people, with the incidence increasing from 0.5% to 8% per year between the ages of 65 and 85 (Ling et al., 2007). This devastating neurodegenerative disorder not only adds to the morbidity and mortality of the affected individual, but it also highly impacts the lives and state of health of their relatives and caregivers (Ling et al., 2007). AD costs Americans an average of $155 billion dollars a year, making it the third most expensive healthcare problem in the country (Khalsa, 1998). As a result of the overwhelming statistics regarding the prevalence of the disease, healthcare expenditure, and the absence of an effective treatment or cure, AD is a recent topic in a great deal of ongoing research.

Science has not yet found a definitive etiology explaining all aspects of the development or disease process of Alzheimer’s disease. According to Berardi et al. (2007) certain pathologies are common to Alzheimer’s patients that do not occur in someone who is aging in a normal manner. The pathological hallmarks of AD include cortical cholinergic neuronal loss and the accumulation of neurofibrillary tangles and amyloid plaques (Berardi et al., 2007). Abnormal changes occur in the temporal and frontal lobes of the brain, as well as associated neocortices and basal forebrain areas. These areas all have direct relation to the development of memory, language, emotions and higher functions of the brain (Friedland et al., 2001). Brain derived neurotrophic factor (BDNF), which is present in high concentrations in the central nervous system of normal adults, is greatly depleted in Alzheimer’s patients. BDNF promotes the growth of basal forebrain cholinergic neurons, serves as a neurotransmitter, and participates in plasticity
mechanisms (Garza et al., 2003). BDNF is an important factor when considering the pathology of Alzheimer’s disease.

According to Alexander and Larson (2007), many older adults notice normal age-related changes in their memory that cause them concern about the development of a form of dementia. These normal changes are not progressive, are very mild and cause only minor difficulties in comparison to the life altering changes of Alzheimer’s disease. The presentation of AD can vary greatly among affected individuals, ranging from slight memory loss to aggression and hallucinations. This is a progressive disorder, affecting individuals at differing rates. Progression to severe dementia is unpredictable, ranging from five to ten years from the onset of symptoms. Early symptoms of the disease are confusion, difficulties with language, reasoning and complex tasks, and problems with orientation and spatial ability (Alexander and Larson, 2007). As the disease process advances, consequently the severity of the symptoms also increases. In later stages of the disease, personality and behavioral manifestations begin to occur as cognition continues to decline. At this stage, many patients may begin to develop anger, aggression, physical violence, hallucinations, and delusions (Alexander and Larson, 2007). In some patients, wandering becomes a concern because patients can become restless with increasing memory deficit. At this point in the disease, safety becomes an issue, and the need for constant care and supervision is often necessary. Patients usually do not die from complications of AD directly, but rather succumb to a secondary illness or an accident related to the disease (Alexander and Larson, 2007).

**Problem Statement:**

Alzheimer’s disease is the most common pathology leading to dementia and the incidence is continuing to increase.
**Purpose:**

The purpose of this literature review was to critically analyze the results of various studies to determine whether certain factors can prevent or delay the neuronal degeneration that leads to Alzheimer’s disease and the theorized mechanisms in which this may occur. Studies examined factors such as physical activity, education level, diet, and head trauma, and their correlation to the age of onset and the rate at which dementia progresses. It was also important to determine whether the progression to Alzheimer’s disease can only be delayed or if there is any evidence stating that it can be prevented. An important focus was to educate people about lifestyle choices they can make to decrease their likelihood of developing Alzheimer’s disease or at least improving their prognosis.

**Design:**

The information for this literature review was based on recent clinical trials as well as retrospective studies of patients previously diagnosed with Alzheimer’s disease.

**Literature Review:**

Due to the lacking treatment options available and the poor prognosis, Alzheimer’s disease (AD) is currently a highly researched subject in this country. Accumulating evidence in the literature suggests that some components of a person’s lifestyle can be associated with neuroprotection, decreasing one’s chance of developing AD. Increased levels of physical activity and education have been inversely associated with the development and progression of AD.
Other areas being studied and showing a negative correlation to AD include diet, vitamin supplementation and hormone replacement therapy.

Human observational studies have been done concerning one’s amount of physical activity and exercise in relation to their risk of developing AD. Such studies are done to determine if people who engage in more physical activity enhance or maintain their cognitive function as they age, thus protecting them against the neural decline leading to dementia. (Larson et al., 2006). In a study of 1740 adults over the age of 65, Larson et al. (2006) assessed their participation in different types of physical activity including walking, hiking, bicycling and swimming. The older adults’ frequency of participation and type of activities were monitored for an average of 6.2 years. The researchers found that 158 of the participants had developed AD and that the participants who exercised greater than three days a week were 34% less likely to be diagnosed with AD than those who did not exercise as frequently. It was found that the active individuals not diagnosed with AD had less of a risk of cognitive decline than the inactive individuals (Larson et al., 2006). Podewils et al. (2004) completed a similar study and found similar relationships between dementia and physical activity. In another study reviewed by Kramer and Erickson, the relationship between walking and the development of dementia specifically in men was evaluated. This study consisted of 2257 male participants between the ages of 71 to 93. The distance walked per day was examined and at a mean follow up of 4.7 years, an assessment for dementia was done. The results of this study found that both walking speed and distance had a negative correlation to the development of dementia (Kramer and Erickson, 2007). Many physiologic explanations for this type of data are presently being considered and tested in rodent studies.
Press and Alexander (2007) suggest that oxidative stress may highly impact the pathogenesis of AD. Upon autopsy, Alzheimer’s patients’ brains have shown lesions that may be caused from excessive free radical exposure. Increased levels of endogenous antioxidants are also found in the brains of AD patients. The Alzheimer’s Disease Cooperative study has suggested that vitamin E, which is an antioxidant, may reduce the toxic beta-amyloid plaques and slow the progression of the disease in previously diagnosed patients. Other vitamins such as vitamin B6, B12 and folate are being studied for similar effects, but have not produced enough convincing data to correlate them with decreasing the risk of Alzheimer’s disease (Press and Alexander, 2007).

**Research Question:**

Are there protective measures, such as physical activity, educational attainment, diet, NSAID use or vitamin supplementation, that will decrease one’s chances of progressing to Alzheimer’s disease?

**Methods:**

Articles with reference to different aspects of Alzheimer’s disease were found using online sources such as Medline, UpToDate, and Ohio Link. Some of the keywords used in searching for these articles included Alzheimer’s disease, prevention, ApoE4, pathology and dementia. Articles were found by using the references of these articles and finding the primary research articles published in various journals.
Definitions:

• Alzheimer’s disease- A chronic, progressive, degenerative cognitive disorder that accounts for more than 60% of all dementias. The most common form occurs in people over 65, but the presenile form can begin between the ages of 40 and 60. The illness causes significant functional disability, and costs more than $33 billion for health care and lost wages in the U.S. every year (Davis, 2005).

• Memory- The mental registration, retention, and recollection of past experiences, sensations, or thoughts (Davis, 2005).

• Dementia- A progressive, irreversible decline in mental function, marked by memory impairment and, often, deficits in reasoning, judgement, abstract thought, registration, comprehension, learning, task execution, and use of language (Davis, 2005).

• Apolipoprotein E, ApoE - A protein that regulates lipid concentrations in plasma and repairs neuronal damage in the central nervous system. ApoE4 allele is associated with early-onset Alzheimer’s disease, probably because it protects neurons less effectively than other ApoE alleles (Davis, 2005).

• Physical activity- A general term for any sort of muscular effort but especially the kind intended to train, condition, or increase flexibility of the muscular or skeletal systems of the body (Davis, 2005).

• Brain-derived Neurotrophic Factor (BDNF) - a protein that acts on certain neurons of the central nervous system and the peripheral nervous system that helps to support the survival of existing neurons and encourage the growth and differentiation of new neurons and synapses. In the brain,
it is active in the hippocampus, cortex, and basal forebrain—areas vital to learning, memory, and higher thinking (Davis, 2005).
Literature Review

Physical activity proves to be a protective measure against AD

Physical and environmental factors associated with the risk of Alzheimer’s disease still remain largely undefined. Although equivocal, evidence from many of the following studies suggests that physical activity may have a relationship with the clinical expression of dementia.

The Cardiovascular Health Cognition Study (CHCS) from 1992-2000 was a prospective study to determine the association between physical activity and the risk of Alzheimer’s disease and vascular dementia. Podewils et al. (2005) comprised a population of 3608 community dwelling men and women age 65 and older, free of dementia at baseline, to participate in the study. The most common 15 types of physical activity in this age group included walking, household chores, gardening, jogging, biking, golfing, swimming and other similar activities. Each of these activities were assigned metabolic equivalents. A leisure time activity questionnaire was completed by the participants regarding the duration and frequency that they engaged in these activities. The kilocalorie expenditure was then calculated for each individual. The diversity of physical activity that each subject was involved in was also documented. Many other covariates were also accounted for in this study. APOE genotyping was done by taking blood samples from the participants. Subjects were grouped into ApoE- e4 carriers and noncarriers, which added another variable to consider in the study. Subjects disclosed their age, gender, height, weight, ethnicity, education level, smoking status, alcohol intake, and use of hormone replacement therapy. Comorbidities of myocardial infarction, angina, stroke, TIA, hypertension, hypercholesterolemia, diabetes mellitus, and congestive heart failure were also disclosed at baseline of the study. The experimenters tried to eliminate as many confounding variables as possible. Two hundred and thirty-three participants were excluded from the study
due to dementia at baseline or a cognitive status that could not be determined. Thus, 3,375 subjects were enrolled in the study. The CHCS classified the subject’s dementia status and type by using a multistage process. Participants were classified by risk and underwent comprehensive evaluations, clinic visits, telephone interviews and cognitive evaluations. The diagnosis of dementia was based on individual performance criteria and then confirmed by a team of neurology and psychiatry experts (Podewils et al., 2005).

The results of this study identified an inverse relationship between physical activity participation and the development of Alzheimer’s disease for ApoE-ɛ4 noncarriers. The relationship did not hold up for carriers of the gene. Evaluations were done on an average of 5.4 years, and a total of 480 subjects acquired dementia in that time. Of the subjects who developed dementia compared to those who did not, they were older, less educated, more likely to be a ApoE-ɛ4 carriers, had worse prior cognitive performance, had more physical difficulties, and were more likely to have pre-existing cerebral disease on MRI. Other confounding variables commonly noted in the subjects that developed AD were a past history of stroke, cardiovascular disease or hypertension (Podewils et al., 2005).

Energy expenditure in kilocalories was inversely associated with the development of dementia, but after the data was adjusted for covariates, there was no longer a significant difference ($p = 0.08$). The number of different activities a subject participated in was also inversely related to the development of dementia, and this relationship remained significant after adjusting for covariates ($p$-trend $= 0.004$). The inverse relationships for both energy expenditure and the number of physical activities and dementia risk were only proven significant in ApoE-ɛ4 noncarriers with a $p$-trend $= 0.001$ (Podewils et al., 2005).
The results of Podewils et al. (2005) identified that physical activity inversely correlates with a person’s dementia risk for ApoE-ε4 noncarriers. In greater detail, they found that there was more significance in the number of different forms of exercise a subject partakes in compared to the frequency, duration, or intensity of the activity with relation to neuroprotection ($p$-trend = 0.004). The researchers hypothesized that participation in various activities requires cognitive skills, such as organization, memory and scheduling which may facilitate the continued use of cortical and synaptic neurons, thus being protective from Alzheimer’s disease. The relationship found between ApoE-ε4 genotype and physical activity in this study implies that the potential benefit of exercise is not great enough to overcome the ApoE-ε4 allele’s ability to induce Alzheimer’s disease (Podewils et al., 2005).

Another study correlating increased physical activity with a decreased incidence of AD is known as The Honolulu-Asia Aging study of 1991-1993. This study was performed by Abbott et al. (2004) with the purpose of examining the association between walking and the future risk of AD, vascular dementia, and overall dementia in older men. Confounding variables that may skew the results of the study were considered and men with poor cognitive function, Parkinson’s disease, stroke, smokers, continued employment, and people using assistive devices to ambulate were excluded from the study. A sample of 2257 men of Japanese ancestry between the ages of 71 and 93 were enrolled in the study. At baseline, genetic susceptibility of the ApoE-ε4 allele was determined. Screenings for cognitive function were used to identify cases of dementia. The preliminary screening was done by the Cognitive Abilities Screening Instrument (CASI), which gave a comprehensive measure of each participant’s intellectual function at baseline. Various tests and a timed walk were used at baseline to determine physical function. Throughout the study, follow up CASI were administered and if the score decreased, a complete assessment for
dementia was done. For a diagnosis of dementia to be given, the participant’s family had to give a history significant for dementia whereby standardized neuropsychological evaluations and neurological exams were used to confirm the diagnosis. Laboratory studies and Computed Tomography (CT) scans were used to classify the type of dementia seen in each participant (Abbott et al., 2004).

The results of the Honolulu-Asia Aging study showed that subjects who walked the most had the highest CASI scores and the lowest decrease in physical activity since mid-adulthood. Physical performance score and years of education tended to be greater in people who walked more. In a mean of 4.7 years from the onset of the study, dementia was identified in 158 cases. Of the positive cases identified, 101 were attributed to AD. For another 27 cases, AD and vascular dementia were combined as contributing factors to the pathology. The incidence of AD was inversely proportional to the amount of miles that a participant walked. The unadjusted incidence for subjects who walked less than 0.25 mile/d was 11.5 ($p = .02$), 10.5($p = .02$) for those who walked between 1 to 2 miles/d, and 5.2 ($p = .06$) for those who walked greater than 2 miles per day. After adjusting for age, men who walked the least (<0.25 m/d) had a 1.8 fold increase than those who walked more than 2 miles/d ($p = .02$). Unlike the CHCS study, the inverse association between walking and dementia persisted regardless of the subject’s genotype for the ApoE- ε4 alleles. An association between walking and other types of dementia were not found to be significant ($p = 0.18$), but the incidence did decrease from 3.3 to 1.1 as the subject’s walking increased to greater than 2 miles/d (Abbott et al., 2004). Also contradictory to the findings of Podewils et al. (2005), the current study found a stronger correlation when considering the intensity and duration of physical activity. In this study, there was an association found between the speed of walking and the incidence of AD, but the association was still not
stronger than the distance walked. Among the men who were able to walk 10 feet in four seconds or less, the incidence of AD was 15.3 per 1000 person years in those who walked one mile/d or less. In men who walked greater than 2 miles/d, the incidence of AD fell to 8.0 per 1000 person years ($p=0.06$) (Abbott et al., 2004). The conclusion of the study suggests that a physically active lifestyle in men help to preserve cognitive function later in life and may decrease their relative risk of AD (Abbott et al., 2004).

**The Effects of Educational Attainment on Alzheimer’s disease**

The inverse relationship between level of education and the risk of Alzheimer’s disease can be explained by two mechanisms. The brain reserve hypothesis implies that all people have a cognitive reserve above threshold for dementia. Education promotes the development of more efficient cerebral activity through the formation of more plenteous and proficient synapses, thus increasing the cognitive reserve. This causes the pathologic neurodegeneration to progress to AD much later in life and delay the onset of clinical symptoms (Munoz et al., 2000). The second mechanism is referred to as the brain-battering hypothesis which suggests that the protective effect of education is mediated through socioeconomic status by reducing physical assault on the brain (Munoz et al., 2000). It is postulated by Munoz et al. (2000) that individuals with higher education have a more privileged socioeconomic status, which can alter the individual’s exposure to factors that pose a risk for the development of AD. These factors include exposure to toxins, detrimental, lifestyle habits, dietary options and access to medical care (Munoz et al., 2000).

Similarly, Fritsch et al. (2001) studied the effects of education on the clinical expression of AD with regard to the age at onset of symptoms, rate of cognitive decline, and length of survival. The researchers hypothesized that higher educational attainment will delay the
symptom onset, slow the rate of progression, and even increase survival in individuals diagnosed with AD (Fritsch et al., 2001). The population sample included 258 subjects enrolled in the research registry of the University Alzheimer Disease Center, Case Western Reserve University, and University Hospitals in Cleveland. The average age of subjects was 73.4 years, the mean education level was 12.8 years, 61.6% were female, and 89.1% were Caucasian. Educational attainment was measured by the highest level of schooling completed. Age at onset and duration of illness were estimated by information obtained from the subjects’ caregivers. Contrary to their hypothesis, the researchers found that higher educational achievement was associated with earlier age at symptom onset ($p<.05$). The extent of this effect was found to be small, with the age at onset only 1.4 months earlier with each year of education completed. As hypothesized, it was found that subjects with advanced education showed a slower rate of cognitive decline ($p<.05$), while those with less education declined more rapidly (Fritsch et al., 2001). An individual who completed 16 years of education had a cognitive decline of 3.6 points per year, compared to someone with 12 years of education who declined 4.5 points per year (Fritsch et al., 2001). At the conclusion of this study, there were 146 deaths used to evaluate changes in length of survival based on education. Educational attainment was not found to be a predictor of increased survival with relation to symptom onset. Incidentally, it was found that women and Caucasians have a longer survival with AD when compared to men and African Americans. Conclusively, the results regarding rate of cognitive decline support the cognitive reserve theory (Fritsch et al., 2001).

In a similar manner, Roe et al. (2008) completed a case series to examine the age of onset of AD symptoms in relation to years of education obtained. The sample was composed of 21,880 participants from the National Alzheimer’s Coordinating Center (NACC) Minimum Data set and
1,449 participants from Washington University (WU) Alzheimer Disease Research Center. The NACC sample consisted of 65% women, 83% Caucasians, and 73% of participants having 12 or more years of education. The WU sample consisted of 63% women, 89% Caucasians, and 68% of participants having 12 or more years of education. Inclusion criteria for both samples were receiving a clinical diagnosis of AD at the most recent clinical assessment and having no missing data on the number of years of education or the age at symptomatic dementia onset. Greater details concerning participant enrollment and assessment of this study have been published by Berg et al. (1998). In summary, the researchers found that the amount of education was associated with earlier onset of dementia symptoms \(p<0.001\). It was also found that the participants with the least educational attainment showed greater dementia severity at first assessment \(p<0.001\). The researcher attributed their findings to the fact that more educated people engage in cognitive tasks on a regular basis, making it easier to recognize subtle changes in cognitive function and thus leading to earlier disease detection (Roe et al. 2008).

In contrast to the case study by Roe et al., Wilson et al. (2002) completed a longitudinal study that evaluates how participation in cognitively stimulating activities affect the risk of developing Alzheimer’s dementia. The sample consisted of 801 Catholic nuns, priests, and brothers from 40 groups across the United States. At baseline, the subjects were required to be at least 65 years old, absent of dementia, consent to annual evaluations, and willing to donate their brain for autopsy. Each subject had an evaluation by a neurologist that included history, neurology exam, assessment of cognitive function, and a brain scan; all of which were repeated annually for the duration of the study. The participants documented their frequency of participation in cognitive activities including watching television, listening to the radio, reading a newspaper, reading magazines, reading books, playing games such as cards or checkers, doing
crossword or other puzzles, and going to museums. A five-point scale was used to rate the subjects participation in these activities and a composite score was determined. At each annual evaluation, 20 different cognitive tests were completed involving episodic memory, semantic memory, working memory, perceptual speed, and visuospatial ability. Participants followed up for a mean of 4.5 years with composite scores ranging from 1.51 to 4.71, with higher scores indicating greater frequency of cognitive stimulation (Wilson et al., 2002). By the conclusion of the study, 111 people developed AD, 101 met criteria for probable AD, and 10 for possible AD. Brain autopsies were done on 31 individuals, of whom 84% met criteria for AD. The relative risk for developing AD decreased by 33% for each point the participant had in the composite measure of cognitive activity (hazard ratio [HR], 0.67; 95% CI, 0.49-0.92). When comparing persons with activity frequency in the 10th percentile, the risk of AD was reduced 28% in a person whose cognitive activity frequency was in the 50th percentile and 47% for participants in the 90th percentile. The analysis was repeated taking the APOE E4 allele into consideration, and the inverse relationship between cognitive activity and dementia remained significant (HR, 0.67; 95% CI, 0.49-0.92). Other medical conditions and clinical depression were also evaluated, but the association was still unchanged. Through this study, Wilson et al. (2002) concluded that a person reporting frequent cognitive activity is 47% less likely to develop AD than someone less cognitively active (p<0.50). The researcher’s hypothesis was accepted suggesting that maintaining frequent cognitive activity in the elderly reduces the risk of developing AD (Wilson et al., 2002).

As long ago as the 2nd century BC, poets and philosophers considered that an active mental life might forestall or delay the enfeeblement of old age (Orrell et al., 1995). The recently described studies have aided in the development of similar theories based on scientific research.
The evidence supports that high educational achievement and continued mental stimulation allow individuals to tolerate more neurodegeneration and cognitive deterioration before symptoms of AD become clinically apparent (Orrell et al., 1995). If cognitive preserve can in fact be increased, the onset of dementia can be delayed and many people may die of other causes before clinical manifestation of dementia symptoms arise, reducing the prevalence of Alzheimer disease (Orrell et al., 1995). Further research is needed for conclusive data, but at present it seems reasonable to recommend that educational attainment and cognitively stimulating activities are worthwhile (Orrell et al., 1995).

**Head Trauma and the Development of Alzheimer’s Disease**

Repeated head trauma in professional boxers has been linked to a syndrome called dementia pugilistica. Neurofibrillary tangles, identical to those present in Alzheimer’s disease, are seen in people with this illness (Roberts, 1988). In an earlier study, Roberts (1991) also described beta A4 protein deposition in the brains of severe head injury survivors, which is also a similar finding on autopsy of an AD patient’s brain. From these findings, researchers hypothesize that head injury can cause the pathological response of beta A4 protein deposition and neurofibrilary tangles leading to the development of AD (Roberts, 1991).

Similarly, Luukinen et al. (2005) completed a 9 year study based on a sample of 1,113 participants, greater than 70 years old and living in Oulu, Finland. Baseline examinations were completed and all participants had a Mini Mental Status Exam score of 27 or better. Educational level, APOE genotype and physical disability were also assessed. Severity of traumatic brain injury (TBI) was categorized into mild TBI, moderate TBI, and severe TBI. At follow-up, 34 subjects were diagnosed with dementia. Sixty-seven percent of these subjects had a moderate TBI, 60% had mild TBI, and 20% were without a history of TBI (Luukinen et al., 2005).
Younger age at symptom onset and detection of dementia was directly related to the incidence of TBI. Subjects that completed less than elementary school level of education also proved to be significantly associated with incidence of dementia ($p = 0.247$). When the presence of APOE genotype was investigated as a contributing factor, it was found to prominently correlate with a younger age of dementia onset. From the data collection, the researchers hypothesize that traumatic brain injury may cause an earlier onset of dementia, increase dementia risk, or activate the onset of AD pathology (Luukinen et al., 2005).

In addition, Sundstrom et al. (2007) completed a five year study to determine if mild head injury increased a person’s risk of Alzheimer’s dementia. They also wanted to assess if possession of the ApoE- ε4 allele and a head insult acted synergistically to increase the development of AD. The study sample included 543 subjects ranging from ages 40 to 85, free of dementia at baseline. Health questionnaires and histories were used to identify subjects with previous head injuries and APOE genotyping was performed on all participants. The results of the study showed that possession of the ApoE- ε4 allele increases a subject’s risk of AD regardless if they had a head injury or not. In participants that did not carry the allele, past head injury did not show an increase risk of dementia ($p <0.001$). In participants who had both the ApoE- ε4 allele and a previous head injury, the relative risk increased to 5.2 ($p <0.001$). People with the APOE genotype and without prior head injury still had a relative risk of 3.0 ($p <0.001$) (Sundstrom et al., 2007). The researchers found that head injury and ApoE- ε4 possession increased a subject’s risk of dementia five-fold compared to subjects with neither of these factors. This study found an association with mild head trauma and risk of dementia, while many other studies only focus on the effects of severe traumatic brain injury (Sundstrom et al, 2007).
A third similar study, completed by researchers Salib and Hiller (1997), also explored the association between head injury and AD in the elderly population. This was a 2 year case control study with the sample population consisting of 538 subjects. These subjects included 198 with the current diagnosis of AD, and control samples of 164 subjects with dementia other than AD, and 176 subjects without dementia. All of the subjects were 65 years or older and referred to an Elderly Mental Infirm (EMI) unit in Warrington, England, after a head injury. The sample included 37.2% males and 62.8% females. The study included patients from different sources that were referred to the psychogeriatrician, thus it was not strictly a population based random sample of participants. Information was collected from each patient regarding their past history, details concerning their head trauma, and age of onset of dementia symptoms. The researchers found an association between head injury with or without loss of consciousness and risk of AD, with a relative risk (Odds Ratio [OR]) of 1.52 ($p<0.05$). This risk did not prove to be specific for AD. For all other types of dementia, the relative risk was 2.36 ($p<0.05$). An increased correlation was not significant when accounting for a genetic predisposition. The increased risk was only significant in male subjects, with no similar risk reproduced in women (OR 2.1, $p<0.05$). This study confirmed that there is a positive correlation between head injury and incidence of dementia, but was unable to prove that it was a risk factor for AD specifically (Salib and Hiller, 1997).

**Dietary and Vitamin Supplements and the Risk of Alzheimer’s Disease**

Oxidative damage to neurons is part of the pathogenesis of Alzheimer’s disease. Zandi et al. (2004) performed a study to determine whether antioxidant supplements can be useful in reducing the risk of developing AD. The study population included 4740 subjects, aged 65 or older, from Cache County, Utah. At baseline ApoE- ε4 genotype was assessed and participants
were categorized according to their use of vitamin supplements. Participants were further divided into Vitamin E users, Vitamin C users, Multivitamin users, or Vitamin B users. At a three year follow-up, 200 prevalent and 104 incident cases of AD were found. In unadjusted analyses, vitamin E, vitamin C and multivitamin users were all inversely associated with AD ($p < 0.05$). After adjustment for age, sex, ApoE-ε4 allele possession, and other confounding variable, the inverse relationship only remained significant for vitamin E and multivitamin users ($p < 0.05$) (Zandi et al., 2004). Use of both vitamin E and vitamin C, with or without a multivitamin, had the strongest inverse correlation with AD prevalence. Concerning the incidence of AD, it was found that use of both vitamin E and vitamin C were negatively correlated. There was no relationship found between a decreased risk of AD and multivitamin use alone, but when added to vitamin E or vitamin C, the trend toward reduced risk became evident. Age, gender, or ApoE genotype did not alter the previously stated associations significantly. The authors concluded that this research confirms that antioxidant supplementation, specifically vitamin E and vitamin C in combination, is a reasonable option to decrease one’s relative risk of developing AD (Zandi et al., 2004).

As previously mentioned, the ApoE genotype has a strong correlation with the development of Alzheimer’s disease. The main function of the Apo E protein is lipid transport; a prevailing sign that lipid homeostasis is an important factor when considering decreasing one’s risk of AD (Friedland, 2003). A diet with a high intake of saturated fat, total fat, and cholesterol has been reported to increase the risk of Alzheimer’s disease. In contrast, increased dietary intake of unsaturated, unhydrogenated fats seems to be protective. The consumption of long-chain n-3 polyunsaturated fatty acids (PUFAs) and docosahexaenoic acid (DHA, omega 3) was associated with reduced risk of developing AD (Friedland, 2003). These can be obtained by
eating foods such as fish, vegetable oils and nuts. There are several mechanisms by which eating fish may be protective against AD development. The PUFAs found in fish are present in reduced levels in the plasma and brains of people diagnosed with AD. The PUFAs are incorporated into atherosclerotic plaques and enhance their stability. Secondly, the polyunsaturated fats in fish and vegetable oils may also lower serum cholesterol and triglyceride levels. It has been suggested that PUFAs may alter the brain’s phospholipid membrane stability and influence amyloid-β precursor protein cleavage. Lastly, it has been reported that rats that are fed PUFAs show a 10-fold increase in transthyretin, which is an amyloid binding protein that enhances β-amyloid protein clearance from the brain, thus adding to the protective effects (Friedland, 2003).

Morris et al. (2003) examined whether fish consumption and dietary intake of different types of n-3 fatty acids protect against the development of Alzheimer’s disease. This was a prospective study conducted from 1993 to 2000 in Chicago, Ill. The biracial sample included 815 participants from the Chicago Health and Aging Project, aged 65 to 94 years. Diet was assessed by means of a modified Harvard self-administered food frequency questionnaire. AD was diagnosed through neurological clinical evaluations that were conducted in each participants’ home by a team consisting of a neurologist, a nurse practitioner, a phlebotomist, and a neuropsychological technician. After a mean follow-up of 3.9 years, 131 subjects were diagnosed with AD, respectively an annual incidence rate of 2.6%. Fish consumption was inversely associated with the incidence of AD. The age-adjusted relative risk for at least weekly fish consumption were in the protective direction, but not statistically significant ($p = 0.18$). This correlation became statistically significant when adjusting for other risk factors including sex, race, education, presence of ApoE-ε4 allele, and total energy intake ($p = 0.07$). Participants who consumed 1 or more fish meals per week had a 60% less chance of developing AD when
compared to participants who reported consuming fish rarely or never (for both groups, relative risk, 0.4; 95% CI, 0.2-0.9). Total intake of the n-3 polyunsaturated fatty acids was inversely related to the risk of AD in both the age and multivariable adjusted models ($p = 0.01$).

Participants in the top five percent of intake had a 70% reduction in risk when compared to persons in the lowest five percent of intake. There was also a decreased risk association with the intake of DHA ($p = 0.02$) (Morris et al., 2003). The researchers further analyzed n-3 fatty acid and fish consumption for evidence of effect modification. It was found that the intake of $\alpha$-linolenic acid was strongly protective in the participants carrying the ApoE- $\varepsilon$4 allele, but there was no association found in individuals who did not possess the allele ($p = 0.02$). Also, total intake of n-3 fatty acid was only protective among women ($p$ for interaction $= 0.02$). Age, sex, race, education, or ApoE- $\varepsilon$4 genotype did not otherwise modify the results. The results of this study suggest that the weekly consumption of fish, vegetable oils and nuts may reduce the risk of developing Alzheimer’s disease (Morris et al., 2003).

**Anti-Inflammatory Agent’s Effects on AD Development**

The amount of inflammation found in Alzheimer’s disease is so extreme that when comparing inflammatory markers of surgically replaced joints, infarcted hearts, or atherosclerotic plaques, the AD hippocampus shows greater upregulation (McGeer and McGeer, 2006). The pathological hallmarks of Alzheimer’s disease are beta amyloid protein plaques and neurofibrillary tangles. Severe areas of inflammation are found surrounding these lesions in the brain of an Alzheimer’s patient (McGeer and McGeer, 2006). Other neuroinflammatory agents are also found in greater quantity in affected areas of the brain. Activated microglia cause neuronal cell death by producing free radicals and proteases. COX-1 is an enzyme that is upregulated in these cells, causing inflammation. The complement system is also activated
causing host cell lysis. These findings lead to the proposal that long term use of anti-inflammatory drugs, such as non-steroidal anti-inflammatory drugs (NSAIDs), can be used to prevent AD (McGeer and McGeer, 2006).

In the Sydney Older Persons Study, Broe et al. (2000) examined the anti-inflammatory drug effects on the risk of AD. Researchers went farther to determine if an anti-inflammatory dose is needed to produce protective effects. The sample was comprised of 536 community-dwelling subjects, age 75 or greater, with an approximately equal number of males and females. A total of 163 patients were diagnosed with dementia, 78 of those being Alzheimer’s disease. The results showed that NSAIDs, aspirin and angiotensin-converting enzyme inhibitors were all inversely associated with AD. It was also found that the protective effects were not dose-related, being that low and high doses were equally protective (Broe et al., 2000). In conclusion, Broe et al. propose that low anti-inflammatory doses are enough to be protective, thus the protective mechanism must occur by a non-inflammatory process (Broe et al., 2000).

**Hormone Replacement Therapy’s Effects on AD**

An overwhelming 15% of elderly women will develop Alzheimer’s disease in their lifetime (Seshadri et al., 2001). Women are at an increased risk of developing AD after they reach age 80 when compared to men of similar age. A decrease in endogenous estrogen in postmenopausal women may account for this increased risk (Zandi et al., 2002). Several mechanisms have been described as attributing to the neuroprotective effects that estrogens pose on the brain. Estrogen inhibits beta-amyloid formation, stimulates cholinergic activity, reduces oxidative cell damage, and helps to protect brain vasculature (Skoog & Gustafson, 1999). Yaffe et al. (1998) reviewed 10 studies and concluded that estrogen may partake in mechanisms that improve cognition, decrease dementia, or decrease the severity of active dementia. The
association between estrogen use and dementia found in several of these studies are summarized in Table 1. The researchers hypothesized several plausible mechanisms of estrogen activity including: modulation of cholinergic neurotransmitters, maintaining or promoting neurons and synaptic plasticity, protection against cerebral ischemia by increasing CNS vasodilation, and decreasing LDL cholesterol and thus atherosclerosis (Yaffe et al., 1998). Treatments to reduce women’s risk of developing AD is an area of great interest.

The Cache County Study, performed by Zandi et al. (2002), examined the relationship between hormone replacement therapy and the risk of AD. The researchers also assessed whether there was a relationship relative to the duration and recency of use. The population sample consisted of 1,375 men and 1,889 women. Participants had a baseline evaluation between 1995 and 1997 for information concerning their hormone replacement therapy (HRT) use status. They were questioned about exposure to HRT and the length of use. At follow-up evaluation three years later, 88 women and 35 men developed AD. Further analysis found that AD was significantly more common for women then for men ($p = 0.002$), but less common for women who previously used HRT compared to those who never used HRT ($p = 0.001$). Duration of HRT was also found to significantly decrease the risk (Zandi et al., 2002). With more than 10 years of HRT, women’s increased risk was decreased completely. There was no reduction in risk of AD in women currently taking HRT, unless they were using it for greater than 10 years. The evidence provided by this study suggests that hormone replacement therapy is protective against the development of AD and can decrease the incidence by more than half (Zandi et al., 2002).
Chapter 3
Discussion & Conclusion

Problem Statement:

Alzheimer’s disease is the most common pathology leading to dementia and the incidence is continuing to increase.

Research Question:

Are there protective measures, such as physical activity, educational attainment, diet, NSAID use or vitamin supplementation, that will decrease one’s chances of progressing to Alzheimer’s disease?

Throughout this literature review, my research question was satisfactorily answered. The various studies found convincing evidence in support of physical activity, educational attainment, diet, NSAID use and vitamin supplementation as protective measures that will reduce one’s risk of developing Alzheimer’s disease.

In the large, prospective cohort study, The Cardiovascular Health Cognition Study, Podewils et al. (2005) identified an inverse association between physical activity and AD risk for ApoE- e4 carriers. These results were not significant in ApoE- e4 noncarriers. Specifically, these results suggest that participating in a variety of different activities may be more important than frequency, intensity and duration of physical activity with regards to dementia risk (Podewils et al., 2005). Neuroanatomical regions of the brain that regulate organizational and memory processes are adversely affected by AD. The involvement of a number of different activities requires organization and memory skills to schedule, attend, and rotate activities, thus strengthening these regions of the brain (Podewils et al., 2005). These researchers, as well as
other experimental studies, have demonstrated that physical activity may protect against AD through several mechanisms. One of these theories is that physical activity facilitates learning, increasing the expression of genes that promote neurogenesis and neural plasticity (Podewils et al., 2005). Levels of brain derived neurotrophic factor (BDNF) are diminished in the hippocampus of AD patients. Research suggests that BDNF plays an important role in mediating exercise induced effects on neuronal structure and integrity. (Podewils et al., 2005). In addition, nonneuronal vascular adaptations are also enhanced with exercise. Examples of these include: increased cerebral blood flow and substrate exchange, increased cerebral capillary density, and decreased accumulation of radical oxidative proteins (Podewils et al., 2005). The researchers also propose that being physically active may be an indication of a healthier lifestyle with fewer factors that may affect cognitive function (Podewils et al., 2005). One of the most important limitations of the study that Podewils et al. disclose is the inability to determine in what period of life physical activity had the most impact on dementia risk (Podewils et al., 2005).

In contrast, Abbott et al. (2004) found that elderly men who walked frequently were less likely to develop AD. Although results should be confirmed, the researchers found that the ability to walk quickly also appears to be associated with reduced dementia risk (Abbott et al., 2004). The researchers propose no mechanism to explain these findings and have no clear explanation for the relationship between walking and dementia. Similarly, the researchers entertain the idea that individuals who walk frequently are more resistant to risk factors and have less lifestyle factors that would lead to increased cognitive decline (Abbott et al., 2004). An obvious limitation to the study is that women were excluded; therefore results were based solely on men. Also, studying a group of men from Hawaii where walking all year is possible, does not accurately describe the behavior of the majority of men elsewhere (Abbott et al., 2004).
In the study by Fritsch et al. (2001) the effects of educational attainment on the clinical outcomes of AD patients were used to test the reserve hypothesis. According to the reserve hypothesis, higher educational attainment provides more and better cognitive and neurological resources that can be used to compensate for the debilitating effects of AD (Fritsch et al., 2001). Based on their research, Fritsch et al. were able to draw several conclusions regarding the impact of education on AD patients. Their findings were inconsistent with the proposed reserve hypothesis being that increased education level was correlated with earlier age of dementia onset by approximately 1.4 months earlier for each educational year completed (Fritsch et al., 2001). The researchers theorize that this finding may be due to the fact that age of symptom onset was based on caregiver reports, and that more educated caregivers could detect subtle symptoms earlier. Also, those with higher educational status generally have better access to medical care, therefore, having the potential for earlier diagnosis (Fritsch et al., 2001). This study also found that patients with higher educational attainment had a slower cognitive decline after the diagnosis was made, which is consistent with the reserve hypothesis. The researchers were unable to conclude that education increased survival, but they did find that female gender and those with later years of birth had a longer survival (Fritsch et al., 2001). The study limitations include excluding patients with possible modifying variables such as use of estrogen replacement therapy, NSAIDs or antioxidants. The ApoE genotype patient sample was too small to provide accurate results. However, Fritsch et al. believe these variables to be unrelated to educational effects, thus not significantly altering the results (Fritsch et al., 2001). The researchers recognize that they were unable to conclude that educational attainment was responsible for slower cognitive decline or if other variables that are correlated with education, such as mental ability,
Likewise, Roe et al. (2008) found that educational attainment was associated with earlier age of onset of dementia. These researchers also suggest that less educated individuals may notice dementia symptoms later and delay seeking medical care (Roe et al., 2008). Patients with greater education partake in more cognitive tasks and have occupational roles that may emphasize the deficits of early dementia, leading to earlier diagnosis of AD. Roe et al. proposed that future researchers may need to change their assessment of less educated subjects to studying memory and thinking problems in cognitive, recreational, and social activities in order to recognize the subtle changes more easily noticed in subjects with greater formal education (Roe et al., 2008).

In contrast to the amount of educational attainment previously discussed, Wilson et al. (2002) concluded that the frequency of participation in cognitive activity is correlated with reduced risk of AD (Wilson et al., 2002). Although this study focused on incident AD and variety of cognitive activities, they also concluded that the frequency of cognitive stimulation was inversely proportionate to the rate of cognitive decline, which is consistent with prior research (Wilson et al., 2002). The researchers suggest that the basis of association between cognitive activity and AD is uncertain, but explore several hypotheses regarding the mechanism of protection induced by cognitive activity. One hypothesis suggests that repetition of cognitive skills lead to less vulnerability to the pathology of AD. Another hypothesis focuses more on the ability to compensate for cognitive decline because of strengthening the processing skills of working memory. Another possibility is that reduced cognitive ability is actually and early symptom of AD. However, the researchers feel they excluded persons with clinical symptoms of
AD prior to the study (Wilson et al., 2002). This study has many strengths including a long study duration, five different evaluations per participant, a follow-up rate of 95%, criteria applied by neurologists, and confirmed AD pathology of 80% (Wilson et al., 2002).

In the study by Luukinen et al. (2005) it was concluded that mild and moderate traumatic brain injuries (TBI) were directly correlated with AD and a younger age of onset in the elderly population. It was found that possession of the ApoE-ε4 allele in association with TBI was correlated to a younger age of dementia detection (Luukinen et al., 2005). Studies have shown that β-amyloid protein deposition occurs in the brain following a lethal head injury in one-third of people. Unlike any other pathology related to injury, the β-amyloid distribution after TBI acts synergistically to increase the risk of AD development (Luukinen et al., 2005). Although all results do not support this view, the researchers suggest that the ApoE-ε4 genotype and TBI also act synergistically to further increase the development of AD. This may be because the Apolipoprotein E alters the brain’s repair mechanism after head injury by affecting the transportation of lipids to regenerating neurons. Specifically, the ApoE-ε4 allele is associated with reduced growth and branching of neurons, thus leading to the development of dementia in the presence of TBI (Luukinen et al., 2005). The data in this study suggests that the brain’s pathophysiologic response to TBI is greater the older the patient is. The researchers consider their study to be reliable due to the representative population sample and their high participation and follow-up rates. They also believe that all traumatic head injuries were included for analysis. Furthermore, the researchers expect larger studies to confirm their results and substantiate the relationship between TBI and the increased risk or triggered onset of AD (Luukinen et al., 2005).

The study by Sundstrom et al. (2007) replicates the results of the previous study. The research demonstrated an association between head injuries and a fivefold increased risk of
dementia in subjects with the ApoE-ε4 allele (Sundstrom et al., 2007). Also, this study did not find that head injury alone increased the risk of dementia. It was concluded that TBI increased the risk of several types of dementia, with AD being the largest and vascular dementia being the second largest subgroup. Being that vascular dementia and AD share similar pathology of vascular lesions, and now including similar risk factors, the researchers propose the need to replicate their study with a larger sample considering subtypes of dementia instead of solely AD (Sundstrom et al., 2007).

In a similar study, Salib and Hiller (1997) illustrated that TBI was positively correlated with the risk of AD as well as all other forms of dementia. However, this increased risk was only found to be significant in males with no significant increase replicated in females. In contrast to previous studies, there was no evidence to suggest that the association was modified by familial predisposition, such as ApoE-ε4 possession (Salib and Hiller, 1997). This study differed in that head trauma did not appear to be a specific risk factor for AD, but rather any form of dementia. The researchers challenge the assumption that AD should be studied as a single condition and feel that future studies should avoid making a similar methodological error (Salib and Hiller, 1997).

In the study conducted by Broe et al. (2001) it was concluded that there was an inverse relationship between aspirin and non-steroidal anti-inflammatory (NSAID) drug use and AD. However, the most significant finding was that these effects were unrelated to drug dosage, with similar results at both high and low doses (Broe et al., 2001). In this study, most participants were taking these medications at low antiplatelet doses, not higher anti-inflammatory doses. This suggests that the low-dose effect of anti-inflammatory medications most likely occurs by a non-inflammatory mechanism (Broe et al., 2001). The major known effects of low-dose aspirin and
other NSAID therapy are on blood vessels and the inhibition of platelets by cyclooxygenase. As cyclooxygenase inhibits platelets, it reduces platelet aggregation and release of platelet factors. Platelets are the primary source of β-amyloid in the blood; therefore, NSAIDs may also directly reduce the amount in circulation. Also, cyclooxygenase produces superoxide radicals within vascular endothelial cells, and decreasing these eradicates β-amyloid-mediated vascular damage (Broe et al., 2001). The researchers discuss that their results have broad significance being that they studied a community-dwelling population of subjects aged greater than 75 years, in which neurodegenerative disorders are likely to occur and drug effects are more common (Broe et al., 2001). The results of this study suggest that the anti-inflammatory drug hypothesis of AD prevention needs to be further studied concentrating on alternative mechanisms of low-dose NSAID and aspirin action (Broe et al., 2001).

The studies conducted in women to determine the effects of estrogen therapy on the development of AD have substantial methodological tribulations leading to conflicting results (Yaffe et al., 1998). Yaffe et al. address some of their concerns regarding the validity of the studies they reviewed, including: the possibility that some controls may have had dementia at the onset of the study, there was no true definition of hormonal treatment, the use of telephone interviews to ascertain information, and diagnoses made on death certificates may be unreliable (Yaffe et al., 1998). All of these are possible confounding variables that the researchers recognize as potentially affecting the reliability of the results. Despite these facts, these studies had primarily positive results while describing conceivable mechanisms by which estrogen therapy may prevent the development of AD or lead to increased cognitive function (Yaffe et al., 1998). In spite of these positive results, the researchers do not recommend estrogen use to prevent AD. Yaffe et al. recommend a large placebo-controlled trial to further address estrogen’s
role in prevention of AD while assessing the known risks of prolonged estrogen therapy (Yaffe et al., 1998).

Correspondingly, Zandi et al. (2002) also discuss how the estrogen studies in women have produced conflicting results due to methodological problems, while still acknowledging that the biological and neurophysiological mechanisms proposed to account for the beneficial effects are reasonable. The researchers’ meta-analysis of the effects of estrogen to protect against AD suggests a 29% decreased risk (Zandi et al., 2002). Although the largest and most methologically sound study reviewed by the researchers showed no benefit of estrogen use on the cognition of women, eight smaller trials provide inconclusive results that estrogen therapy was beneficial. Unfortunately, Zandi et al. found these studies susceptible to confounding variables. For example, women choosing to take estrogen replacement therapy were often more educated and healthier than nonusers, which may have resulted in a lower initial risk of developing AD regardless of estrogen use (Zandi et al., 2002). However, given the lack treatment options in women diagnosed with AD and the potential estrogen benefit, the researchers also believe that a large randomized trial of estrogen therapy to increase cognitive reserve and decrease dementia should promptly be completed (Zandi et al., 2002).

The analyses the Cache County Study, by Zandi et al. (2004) examined the degree to which vitamin supplements were associated with the occurrence of AD. The researchers found that vitamin E in combination with vitamin C is associated with reduced incidence of AD. There was no notable risk reduction with vitamin E or C alone, or with the use of B-complex vitamins (Zandi et al., 2004). The Institute of Medicine currently recommends a daily allowance of 22 IU (15 mg) of vitamin E and 75 to 90 mg of vitamin C. Multivitamins usually contain these minimal quantities, while individual doses typically contain 1000 IU of vitamin E and 500 to 1000 mg of
vitamin C (Zandi et al., 2004). Therefore, the findings of this study suggest that vitamin E and C may be protective of AD when taken together as individual supplements due to the higher dosages. These findings may occur because vitamin E is one of the strongest antioxidants that reduces oxidative stress-related damage associated with the pathology leading to AD. The use of vitamin E, being water soluble and rapidly excreted, may be limited to the reduction of vitamin E after it has been oxidized (Zandi et al., 2004). The authors suggest that randomized prevention trials are warranted for formal confirmation that the combination of vitamin E and C may prevent AD (Zandi et al., 2004).

In the study by Morris et al. (2003) the consumption of n-3 polyunsaturated fatty acids and fish were associated with decreased risk of AD. There was a 60% decrease in persons who consumed fish at least once per week compared to those who rarely or never ate fish (Morris et al., 2003). Of the marine n-3 fatty acids, only DHA, a major component of brain phospholipids, proved to be protective. DHA has also been studied extensively for its antiatherosclerotic properties. The n-3 polyunsaturated fatty acids have profound effects on membrane functions, leading to change in nerve conduction, neurotransmitter release and uptake, and postsynaptic transmitter effects (Morris et al., 2003). The researchers conclude that the consumption of fish, vegetable oil, and nuts at least once per week reduce the risk of developing AD. This information provides a strong basis for further study through epidemiologic investigations and clinical trials (Morris et al., 2003).

**Conclusion**

Given that Alzheimer’s disease is the most common form of dementia and the incidence continues to increase yearly, studies to prevent or delay the pathology are of vast importance. The purpose of this literature review was to analyze many studies that attempted to identify
factors that may prevent AD and to better understand the mechanisms by which they occur. A
great deal of evidence throughout the literature suggests that some components of a person’s
lifestyle can be associated with a decreased chance of AD. Increased levels of physical activity
and educational attainment have been inversely associated with AD with the most convincing
results through various studies. Head injury, NSAID use, vitamin E and C combination
supplement use were also convincingly found to be negatively correlated to the development of
AD. Estrogen replacement therapy studies in older women resulted in the most varying
conclusions and are in need of further study before recommendations can be made.

In summary, participation in physical activity is protective against the development of
AD. Both increased frequency and engaging in a number of different activities have protective
properties. In many of these studies, the inverse relationship was only significant in ApoE-ε4
allele carriers. I do not believe that this should impede recommendations of increased physical
activity because average people are unaware of their genotype and would benefit from increased
activity in many ways, regardless of their allele status. Physical activity is already recommended
to enhance cardiovascular health and help maintain quality of life in older adults. The inverse
relationship between physical activity and decreased dementia risk may provide additional
incentive for people to become or remain active as the age.

With regards to education, my research supports the hypothesis that higher educational
attainment affects aspects of clinical expression of AD. Both the cognitive reserve theory and
brain-battering hypothesis have methodologically explained the relationship between a higher
education level and the decreased risk of AD. Due to similar possible confounding variables
identified in many of the studies, future clinic-based research controlling for cohort and period
effects, baseline dementia severity and duration of illness, and duration of participation is warranted.

Similarly, I agree with the hypothesis that TBI may hasten the onset of AD, increase the risk of dementia, or even trigger the onset. In this case, the ApoE-ε4 allele is a strong indicator, being that it further impairs the central nervous system’s repair after injury. It was proven that TBI and ApoE genotype act synergistically to trigger the onset of dementia in those previously free of the disease. The main conclusion drawn from these studies is that strong measures should be taken to avoid TBI amongst the elderly in order to prevent AD. Further research should consider the frequency of head traumas and the duration between the head injury and the onset of cognitive changes.

Also with convincing evidence, there was an inverse association between NSAID and aspirin use and development of AD. There was no evidence of dosage effect, being that equivalent results were obtained in participants using both high and low doses. Surprisingly, most participants were taking doses low enough to suggest that the positive results were not entirely due to anti-inflammatory mechanisms. The anti-inflammatory drug hypothesis of AD prevention needs to be further studied concentrating on alternative mechanisms of low-dose NSAID and aspirin action.

Although many confounding variables and methodological problems have been scrutinized in many of the estrogen therapy trials, I believe that the biological and neurophysiological mechanisms that lead to beneficial effects on cognition and a reduced risk of developing AD are plausible and do in fact deserve greater research. Due to the concerns of increased risk of endometrial cancer, invasive breast cancer, stroke, and deep vein thrombosis associated with estrogen therapy, I believe that use of estrogens to improve cognitive function
and decrease dementia progression in individuals already diagnosed with AD would be better than prophylactically using estrogens to prevent AD. In patients with an increased risk of these diseases, estrogen therapy should be disregarded, even in those using it to slow the progression of AD. Similarly, in patients with increased risk of AD, such as possession of the ApoE-ε4 allele, estrogen therapy may be used more liberally to prevent dementia development.

Final areas that strongly suggest the need for further investigation and clinical trials are the effects of diet and vitamin supplementation on AD development. Studies suggest that vitamin E and C may be protective of AD when taken together as individual supplements due to the higher dosages. These findings may occur because vitamin E is one of the strongest antioxidants that reduces oxidative stress-related damage associated with the pathology leading to AD. The consumption of fish, vegetable oil, and nuts at least once per week reduces the risk of developing AD. The results of these studies are convincing in that making these recommendations seems feasible, while the need for further study still exists.

In conclusion, I feel that science has made great strides in the prevention and delay of Alzheimer’s disease, but where the problem lies is giving individuals the necessary information to be active in prevention. Just as people are given the knowledge to reduce their risk of cardiovascular disease, they should have equal access to the recommendations made in these various studies to prevent against AD. With the exception on estrogen use, all of these factors can be implemented without otherwise causing the patient harm. It is now our job as healthcare providers to educate patients in give them the tools to reduce their risk of developing such a devastating disease.
References


Patients with Alzheimer’s disease have reduced activities in midlife compared to healthy control-group members. *Proceedings of the National Academy of Science, 98*, 3440-3445.


Table 1 – Case-Control Studies of the Association of Estrogen Use and Dementia*

<table>
<thead>
<tr>
<th>Source, y</th>
<th>Cases</th>
<th>Controls</th>
<th>Covariates†</th>
<th>Outcomes</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heyman et al., 17, 1984</td>
<td>4 Definite and 3 Probable AD; 15%</td>
<td>2 Community controls per case, 8% taking ERT</td>
<td>Age, education, and Place of residence</td>
<td>OR, 2.4 (95% CI, 0.7-7.8 $) for Current estrogen use compared with no current use</td>
<td>Some controls may have had Dementia</td>
</tr>
<tr>
<td>Amaducci et al., 18, 1986</td>
<td>116 Probable AD; 12% taking ERT</td>
<td>97 Community controls; 8% taking ERT</td>
<td>Age and region of residence</td>
<td>OR, 1.7 (95% CI, 0.4-5.9 $) for “use of estrogens in menopause” compared with never use</td>
<td>No information about estrogen use in almost half of cases and controls</td>
</tr>
<tr>
<td>Broe et al., 19, 1990</td>
<td>83 Probable and 87 possible AD; 8%</td>
<td>170 Community controls; 11% taking hormones</td>
<td>Age and region of residence</td>
<td>OR, 0.7 (95% CI, 0.4-1.6 $) for &gt; 6 mo of “hormonal treatment” compared with no use</td>
<td>No definition of hormonal treatment</td>
</tr>
<tr>
<td>Graves et al., 20, 1990</td>
<td>130 Probable AD; 18% taking ART</td>
<td>130 Friends and relatives of cases; 16%</td>
<td>Age</td>
<td>OR, 1.2 (95% CI, 0.5-2.6) for estrogen use at the same time of symptom onset compared with no use</td>
<td>Telephone interview to ascertain estrogen use</td>
</tr>
<tr>
<td>Brenner et al., 21, 1994</td>
<td>107 Probable or definite AD; 7%</td>
<td>120 Community controls; 48% taking ERT</td>
<td>Age and hysterectomy status</td>
<td>OR, 1.1 (95% CI, 0.6-1.8 $) for ever use of any estrogens compared with never use</td>
<td>Estrogen use based on recorded prescription data</td>
</tr>
<tr>
<td>Henderson et al., 22, 1994</td>
<td>73 Probable and 70 definite AD; 7%</td>
<td>92 Community controls; 16% taking ERT</td>
<td>Age and education</td>
<td>OR, 0.3 (95% CI, 0.1-0.8) for current oral estrogen use compared with no current use</td>
<td>Cases taking estrogen had better cognitive scores than those not taking estrogen (P=.02)</td>
</tr>
<tr>
<td>Paganini-Hill and Henderson, 23, 1994</td>
<td>71 Cases with AD and 65 with other dementia diagnoses on death certificates; 36% taking ERT</td>
<td>4 Controls who had died per case; 46% taking ERT</td>
<td>Age, age at menarche and at menopause weight, type of menopause, antihypertensive medication, stroke</td>
<td>For AD, OR, 0.7 (95% CI, 0.4-1.2 $) for ever use of estrogen compared with never use; for other dementia diagnoses, OR, 0.7 (95% CI, 0.3-1.1) for ever use of estrogen compared with never use</td>
<td>Diagnosis based on death certificate that may be unreliable; case control study nested in Leisure World cohort of 8877 women; hormone use was ascertained by questionnaire 91 mo before death</td>
</tr>
<tr>
<td>Mortel and Myer, 24, 1995</td>
<td>93 Probable AD† and 65 probable vascular dementia; 11% taking ERT</td>
<td>148 Friends and relatives of cases and caregivers; 20% taking ERT</td>
<td>Age</td>
<td>For AD, OR, 0.6 (95% CI, 0.3-1.2 $) for current oral estrogen use compared with no current use; for vascular dementia, OR, 0.5 (95% CI, 0.2-1.2) for current oral estrogen use compared with no current use</td>
<td>Only study to include vascular dementia</td>
</tr>
</tbody>
</table>

*AD indicates Alzheimer disease; ERT, estrogen replacement therapy; OR, odds ratio; and CI confidence interval.
†Covariates defined as variables either matched or statistically adjusted for in the analyses.
‡Alzheimer disease was diagnosed using National Institute of Neurologic and Communicative Disorders and Stroke—Alzheimer’s Disease and Related Disorders Association criteria.
§Confidence intervals calculated from adjusted data from study.
¶Confidence intervals obtained from authors.

(Yaffè et al., 1998).
Abstract

Objective:
The purpose of this literature review was to analyze the results of various studies to determine whether certain factors, such as physical activity, education level, diet, and head trauma, can prevent or delay the neuronal degeneration that leads to Alzheimer’s disease.

Method:
Articles with reference to different aspects of Alzheimer’s disease were found using online sources such as Medline, UpToDate, and Ohio Link, and their references were used to find primary research articles.

Results:
The various studies found convincing evidence in support of physical activity, educational attainment, diet, NSAID use and vitamin supplementation as protective measures that will reduce one’s risk of developing Alzheimer’s disease.

Conclusion:
Evidence has supported that physical activity, educational attainment, diet, NSAID use and vitamin E and C supplementation used prior to dementia onset would be beneficial in reducing one’s lifetime risk of AD or delaying the progression of dementia.