

Alzheimer's Disease  
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The prevalence of Alzheimer's Disease (AD), a degenerative and currently incurable disease, is on the rise. If you don't currently know someone personally who is dealing with this disease, the odds are that you soon will. In 2010, the figures for AD were as follows: 5.3 million people have the disease, it is the 7<sup>th</sup> leading cause of death, \$172 billion are spent annually on the disease, and there are 10.9 million unpaid caregivers giving their time to those with AD who need their assistance (Alzheimer's Disease, Facts and Figures 2010). The greatest risk factor for AD is age. The majority of those with AD are age 65 and older. The risk of developing AD doubles for every 5 years after the age of 65 (Bettelheim, 1998). It is predicted that this age group is about to get significantly bigger, with the first of the baby-boomer generation reaching 65 this year. By 2029, all baby boomers will be at least 65 years old. This means that the number of people who either have AD or are at a very high risk for developing the disease is going to increase dramatically. It will soon be a very well known disease because virtually everyone will affect everyone through a family member or another close relation. This literature review will explain what Alzheimer's Disease is, what is known about it at this point in time, what can be done, and where the research is headed.

### **History**

Alzheimer's Disease is not a new disease, but is only recently becoming a public health issue. The Ancient Greeks and Romans described the disease symptoms, and cognitive declines, according to Bettelheim-- so it has been around for a very long time. The disease was officially named in 1906 after a German neuropathologist named Alzheimer. He was working with a 51-year old female patient who suffered the now

classical and well-known symptoms of AD (Bettelheim, 1998). Until recently, the disease was not a threat to public health because it was rare for people to live to the age of 65, and people were dying of other illnesses long before the symptoms of AD would begin to surface. Now that people are living much longer (on average 78 in the U.S.), diseases that have later onset are becoming commonplace and must be dealt with in both personal and public health settings.

### **Cause**

Alzheimer's Disease is the most common type of dementia. Dementia is defined as "the loss of or decline in memory and other cognitive abilities" (Alzheimer's Disease, Facts and Figures, 2010). The brain forms structures, called plaques and tangles, that are not present in a healthy, young, normal brain. Plaques are "accumulations of beta-amyloid protein in the extracellular space" (Binton & Yamazaki, 1998). Tangles are "intracellular fibrils formed mainly by paired helical filaments linked together by hyperphosphorylated tau protein" (Binton & Yamazaki, 1998). Together, these two abnormal structures are what cause the dementia associated with Alzheimer's disease. Beta-amyloid and tau proteins are not normally present in abundance in the brain. When they accumulate, they cause blocks in neuron-communication, which ultimately leads to death of certain parts of the brain due to lack of blood flow and neural activity. In a healthy brain, tau protein keeps the neural tubes open so that neural signals can travel quickly and properly. When these turn into tangles, these pathways are shut down. Beta-amyloid buildup was researched in a recent study in which normal, healthy brains and those with AD and severe beta-amyloid angiopathy (which means diseased blood vessels due to an increase of beta-amyloid protein) were compared. All brains were stained with

immunogold silver staining for beta-amyloid-40 and beta-amyloid-42, which are biomarkers associated with AD. This stain was used with electron microscopy. Colloidal gold particles attach to specific proteins (in this case, beta-amyloid), and label them with a dark appearance. The beta-amyloid 40 and 42 deposits were seen throughout the brains in the smooth muscle cells, with 42 more abundant in vessel walls, and both present throughout the capillary walls, but only in those patients with AD. The control brains did not have the beta-amyloid 40 or 42 deposits anywhere. Researchers concluded that the protein deposits are located in drainage pathways, therefore blocking them ("New Alzheimer Disease Study Results from University of California Described", *Science Letter*, 2011). This ultimately leads to the death of brain cells and deterioration of the tasks that part of the brain was responsible for performing. The plaques and tangles first occur in areas in the brain where memory functions take place (Alzheimer's Association, *The Basics of Alzheimer's Disease*, 2010). The reasoning for this is not known, and although some plaques and tangles are found in all aging brains, individuals with AD have significantly more of these buildups in much more concentrated areas (memory functioning areas are the first to die), resulting in vast cell damage and death in the brain.

Since the brain of someone affected by AD cannot be physically tested and examined until they are deceased, it is hard for researchers to come to a conclusion as to what leads to this disease. Plaques and tangles are seen in the brain dissected after death, but what causes these plaques and tangles to form is yet to be determined. The buildup of beta-amyloid protein is what is leading to the dementia that comes with AD, but what is leading to the over-accumulation of the protein? There are many theories why these proteins are present in such great amounts, but researchers are still working towards the

exact cause. Researchers and doctors have found what they refer to as pre-amyloid plaques, meaning that it is a buildup process, and those suffering from the disease accumulate this amount of the protein over time—they are not born with higher amounts of beta-amyloid and tau than those without AD (Selkoe, 2001). Something is triggering this accumulation, and it seems to happen as the brain ages, but it is a progressive process that occurs over time. The deterioration in brain cells is accompanied by a drop-off in acetylcholine production (a neurotransmitter that plays a large role in cognitive functioning). This further progresses the disease symptoms and adds to the physical damage of the brain cells.

### **Genetics**

Some cases of AD can be genetically linked, but it is much less common than the “sporadic” cases that occur without family history or genetic predispositions. The familial form of AD usually has an earlier onset, before the age of 60. It is passed on through autosomal dominance (meaning that only one parent needs to pass on the gene, not both, for the disease to occur), and is “linked to mutations in three genes: amyloid precursor protein (APP), and the presenilins one and two (PS1, and PS2)” (Binton & Yamazaki, 1998). Mutations on PS1 cause the majority of the familial cases, APP mutations cause some of the cases, and mutations on PS2 are very rare. The PS1 mutation causes problems with cell cycle and mitosis. The APP mutation is found on chromosome 21 and makes beta-amyloid, which is what makes up the amyloid plaques. People who have Down’s Syndrome have three copies of chromosome 21, resulting in more APP (and therefore more beta-amyloid protein) Thus; they develop AD symptoms at a young age (in their 20’s or 30s). Much of the current research on AD is focusing on the similarities

between Down's Syndrome and AD in terms of the genetically mutated APP production. Since Down's Syndrome has been a public health issue for longer than AD, more is known about Down Syndrome than AD at this point in time. The APP commonality can be used by AD researchers to further understand what is genetically occurring and why. Research on the genetic type of AD is helpful in discovering the origin of the disease. However, the genetic version is not as common as the sporadic cases, leaving many unknowns for those who get AD without genetic predisposition. There are also other types of genetically inherited mutations that are linked to AD, but they are even less common, some specific mutations affect only a few families worldwide (it is possible that more families are affected but not properly diagnosed, or some families do not live to the age of onset of AD). Sporadic cases may have genetic links as well, the specific mutations are just not known yet. The mutations could be acquired throughout the lifespan (possibly coming from damage to brain from concussions or other injuries, or exposure to some sort of chemical toxins), and could cause genetic mutations that produce AD.

### **Symptoms**

The symptoms of AD include cognitive decline (memory loss, decline in language, judgment, planning and organizational abilities), and behavioral changes such as irritability, anxiety, or depression. The rate of decline is different on an individual basis, but in all cases, the disease gets progressively worse. AD is broken into different "stages" based on the symptoms the individual is experiencing and their cognitive abilities at that time. According to the breakdown of the stages by the Alzheimer's Association's "Basics of Alzheimer's Disease, 2010", stage one has no impairment, and

the cognitive decline progresses, until the late stages, where sleep problems, wandering, agitation, or hallucinations may occur. Stage seven is the final stage, and the individuals here cannot function on their own in daily activities. They may lose the ability to communicate with others, eat, hold their head up, have normal muscle reflexes, and swallow. These stages are used as a way for doctors to determine how far along the patient is with the disease progression based on their amount of cognitive functioning.

AD is the seventh leading cause of death in the United States, and “death usually occurs within three to nine years after it is diagnosed” (Harvard Medical Health Letter, 2010). Individuals with AD do not necessarily die directly of the damaging effects Alzheimer’s has on the brain, but of the inability to function normally in daily life or of other illnesses whose effects are made worse by the Alzheimer’s. AD complicates their other illnesses and makes treatment for those diseases very difficult. AD individuals have a hard time remembering to take their medications, especially to take them at the correct time. When a patient is seen for another illness and they have memory loss due to AD, they often are not able to give complete medical histories, and expensive diagnostic tests have to be repeated if there are lapses in their medical charts. This adds to the high monetary costs of the disease. Those with Alzheimer’s eventually lose the ability to do activities of daily living that would contribute to their overall health (eat well, exercise or other forms of movement, practice of good hygiene, etc), and they lose much of their quality of life. The majority of those with AD die due to pneumonia because they lose the ability to swallow on their own, and feeding can cause problems with fluids and infections in the lungs (Alzheimer’s Association, Facts and Figures, 2010). Another thing to consider when looking at statistics on death due to AD is that it may be

underrepresented because of the reporting protocols on death certificates. As mentioned, Alzheimer's may not be the direct cause of death if someone dies of pneumonia while also suffering the effects of AD (although they may have avoided the pneumonia altogether or been able to fight it off had AD not taken hold). It can be a confusing distinction between dying of Alzheimer's, and dying with Alzheimer's. It would be helpful if 'cause of death' on death certificates were dealt with more consistently with people who have underlying chronic diseases such as Alzheimer's.

### **Risk Factors**

The cause of AD and the specific cause of the plaques and tangles buildup are not yet known, but it is thought to be a combination of multiple factors. Risk factors are age (the risk increases as one reaches the age of 65, and then keeps increasing from there), genetic predisposition (causes early-onset AD), and having mild cognitive impairment (MCI). MCI is defined as "problems with memory, language or other essential cognitive function that are severe enough to be noticeable but not severe enough to interfere with daily life" (Alzheimer's Association, Facts and Figures, 2010). Women have a higher prevalence of AD, but women also live longer than men on average. Therefore, it follows that more women will have the disease than men, simply because there are more women than men living over the age of 65. According to The Alzheimer's Association's Facts and Figures 2010, socioeconomic status also plays a role in the risk of developing AD. An example of this is the inverse relationship between years of education and risk for AD. Also, the health of the brain is linked to the health of the whole body, especially the cardiovascular system, in particular the heart muscle. Just as illnesses and diseases of the cardiovascular system are more prevalent in those of lower socioeconomic statuses, so is



AD. African-Americans and Hispanics have AD at much higher rates than Caucasians. This is most likely tied to overall health and healthcare access (determined by socioeconomic status) than to their race.

### Care

Alzheimer's Disease causes a huge burden on those dealing with it because it becomes so debilitating, and much assistance is needed. The person with AD has a degeneration of their cognitive abilities and is unable to care for themselves during later stages. They become reliant on others to care for them, and this can be a difficult job. The cost of this disease is very high, and "people with AD are high users of health care, long-term care and hospice" (Alzheimer's Association, Facts and Figures, 2010). Caregivers are often family members, and are unpaid. These caregivers put in a lot of unpaid hours, and lose out on money they could be earning putting that time into their own work. They also have a lot of added stress and workload in their lives, lowering their own health status. The cost to caregivers is high, and on top of that, there is a huge cost to the health care system. The majorities of people with AD are over 65 years of age, and therefore are also on Medicare. According to the 2010 Facts and Figures, the annual living costs for those with AD are three times higher than an individual without AD. These costs stem from hospital care, medical providers, nursing homes, home care, and medications.

Kiecolt-Glaser, et al conducted a study in 1991 on the affects of care-giving for an AD patient on the care-taker's immune system. The majority of care-givers are family members, especially the spouse, if still living. The study assessed 69 spousal care-givers who had been giving care for an average of five years in comparison with control subjects. Initial and follow-up data (an average of 13 months later) were collected

regarding immune function. Caring for a spouse with AD is considered a chronic stressor because the disease progresses over a period of years. The results were that the care-givers had significantly higher rates of depression, felt that they had less support from others, less people in their support network, and the largest difference was seen in the immunological tests. Caregivers had higher prevalence of days ill from infectious disease (mostly upper respiratory tract infections), and their immune health declined between the initial and follow-up data, meaning that the care-givers health declines as the disease progresses. It may be thought that it would be less stressful and easier on the caregiver to put their spouse in a nursing home, but this study saw that those who had institutionalized their spouse over the course of the study had the highest negative immune changes. This is a very hard thing for the caregiver to do, and this shows that it has a very strong effect on their own health and well-being.

### **Delay of Onset**

According to Bettelheim, at this point in time, four million Americans have Alzheimer's disease, and this is projected to increase to 14 million by 2050 unless a cure is discovered. Delaying the onset of the disease would have a lot of impact on the total statistics of the disease prevalence, and the public health implications would be enormous. Researchers, such as Brookmeyer et al., are turning their focus towards putting off the start of the disease progression rather than only focusing on finding a cure for those already dealing with AD. Even a small delay of onset would have considerable effects on the overall number of people living with the disease: "If onset could be delayed, on average, only 6 months, there would be nearly 100,000 and 380,000 fewer persons afflicted with Alzheimer's disease than projected after 10 and 50 years,

respectively” (Brookmeyer, Gray, & Kawas, 1998). This large of a decrease in people affected would also lower the monetary burden of AD. Preventative measures can be costly upfront, but as these numbers show, a small delay in onset (6 months) has huge decreases in numbers of people living with AD, and the money saved in the long-term would outweigh the initial costs put toward prevention and delaying onset.

### **Drug Therapy**

Even though more than \$3 billion of federal money has been spent on Alzheimer's research since 1976, scientists have only been able to develop a few drugs approved by the Food and Drug Administration that may slow the progression of the disease. Tacrine and donepezil have been found to temporarily delay the breakdown of acetylcholine and boost the levels of this neurotransmitter in the brain. But, neither of these drugs can restore memory nor reverse the disease's pattern of killing brain cells (Bettelheim, 1998). The drugs all have side-effects and many warnings, and none have significant success stories. Other strategies for slowing the progressions of the disease are: hormone (estrogen) replacement therapy for women, using non-steroidal anti-inflammatory drugs, and antioxidant therapy.

Estrogen has neuroprotective effects against the damage done by the built up beta-amyloid proteins (Binton & Yamazaki, 1998). Estrogen replacement increases blood flow to the brain, which keeps the brain running with adequate oxygen and glucose. The “Battle for Your Brain”, a Tufts University Health and Nutrition Letter published in 2010, brought to attention that the different areas that women carry their excess weight make a difference in their rates of AD risk. Women who carry more weight on their hips rather than in their abdominal area showed to have lower cognitive abilities, and

increased risk for AD. This could be due to fat cells in the abdomen releasing estrogen, which has been shown to have neuroprotective effects (Tufts University Health and Nutrition Letter, 2010).

Anti-inflammatory drugs have been shown to reduce the risk of AD. “Immune type cells, microglia, the nervous system’s equivalent to the macrophage, and microglia released immune signals are found within beta-amyloid plaques” (Binton & Yamazaki, 1998). This inflammatory response only magnifies the plaques and the damage they cause to the neurons. Taking an anti-inflammatory could reduce this extra chaos occurring at the plaque sites. Plaques are part of normal brain aging, but in small amounts, and it only becomes a problem when these plaques appear in vast numbers and sizes.

Antioxidants can be used as a preventative strategy because they help rid the brain of the free radicals that are present due to the oxidative metabolism that takes place. Oxidative damage increases with age, just as risk for AD increases. Keeping the brain healthy and free of metabolic byproducts would be beneficial in reducing risk for AD. According to Binton & Yamazaki, antioxidant therapy appears to be able to slow the degeneration in individuals with AD, but does not restore function that has already been lost. Concerning diet, Vitamin E from food sources rather than supplements, shows positive results in antioxidative capabilities in the brain. “Vitamin E is a lipid-soluble vitamin that interacts with cell membranes and traps free radicals, thereby protecting lipid membranes from oxidative damage” (Binton & Yamazaki, 1998).

## **Early Detection**

AD is a progressive disease, and is usually hard to detect in the beginning stages. It is often hard to tell whether a person has another form of dementia or AD. The benefit in early diagnosis is planning ahead, and start of therapies that slow the progression. When an individual is not diagnosed with AD until later stages, it may be beyond their ability to make important decisions (especially regarding their finances, housing situation, and how they would like their course of care to go).

Just last year, doctors began to use two diagnostic tests that are extremely accurate, a huge improvement from the ambiguous tests previously used. The first of these is injection of radioactive dye into the patient's brain, which attaches to amyloid protein plaques, and then a PET scan is taken that shows the dyed areas. The second test is to take out cerebrospinal fluid (CSF) from the spine with a syringe and test it for the presence of amyloid and also tau, both proteins present in AD patients' CSF. The New York Times recently published an article titled "FDA Sees Promise in Alzheimer's Imaging Drug" describing the new approval of using the dye that highlights plaques in the brain and shows up on PET scans. It will now be easier for doctors to diagnose those with memory loss symptoms as either having AD, or some other form of dementia. This will be helpful because if the scan shows no plaques (no AD), the treatment can focus on other things that may be leading to the dementia. If there are plaques seen in the PET scan (AD present), then the patient and their family can try both drug and non drug avenues for stalling the growth and spread of plaques and they can also begin to plan ahead for the later stages of the disease, which can be extremely tolling. Many of the available treatments are given so late in the disease progression that they do not help

much at all, but these new diagnostic tools will change this and they will be much more effective if given at the very early onset of disease. This is a huge step forward, and the medical community is very excited for the future of their diagnostic abilities.

### Exercise

The use of exercise prescription to patients with AD is suggested by the Alzheimer's Association to enhance their quality of life, decrease depression rates, and maintain cognitive abilities. Studies are now showing that exercise not only increases quality of life for those living with AD, but also may contribute to disease prevention. Research by Liang, et al used certain biomarkers of AD to test whether those who exercise more have a significantly lower amounts of these AD precursors. Beta-amyloid plaques can be seen through PET scans when using a compound that is taken up by the protein. Cerebrospinal fluid levels of beta-amyloid and tau proteins are indicative of AD, as well as brain atrophy, as seen through MRIs. The subjects were interviewed about their physical activity levels, and the biomarkers were tested for. The results of this study showed that the sedentary individuals were more prone to developing AD (Liang et al 2010).

Another study, conducted by Hoveida et al in 2011, showed that exercise has beneficial effects in regards to the cognitive decline during AD progression. This study was done on wistar rats that were representative of Alzheimer patients because their brains were infused with ibotenic acid dissolved in phosphate buffered saline. The control mice (without AD) only had saline solution injected into their brains. The rats were put in mazes to test their cognitive abilities. The AD rats were split into two groups: those that got exercise via treadmill running, and those that got no exercise. The mazes had water,

and the rats had to swim to platforms, that were moved during different phases of the experiment to new areas to test if the rats remembered where the platform used to be. The group of AD rats that got exercise showed better memory and showed less of the destructive effects of the acid on the brain. It concluded that treadmill running in these rats had both therapeutic and preventative effects. This is really beneficial evidence that exercise can be used in the prevention of AD human patients.

Most evidence thus far indicating what is healthy for the brain follows what is healthy for the heart. This makes sense because the heart fuels the brain with the oxygen and energy it needs to function. So, if the heart is healthy, the brain should be as well. Exercise and a healthy, balanced diet is the best way to keep the cardiovascular system working at it's full potential. Not only are the baby-boomers entering the age of high risk of AD, but with aging comes the increased risk of many chronic cardiovascular diseases. In the US, heart disease is the number one killer, and there is an obesity epidemic occurring, causing higher rates of diabetes and other ailments. The metabolic syndrome (also known as "syndrome x") is composed of five cardiovascular risk factors: abdominal obesity, hypertriglyceridemia, low high density lipoprotein (HDL) levels, hypertension, and hyperglycemia (Yaffe, 2007). There is a dangerous cycle of sedentary living habits and high-fat, easily accessible and abundant foods in current culture that is leading to diseases that should be preventable. Advances in medicine have increased average lifespan, and decreased mortality due to infectious diseases. These chronic, non-communicable diseases that syndrome x predisposes, are the new threat to health. Metabolic syndrome encompasses many of these problems into one name because cardiovascular disease is multi-factorial. When the heart and blood vessels are weakened,

the brain suffers as well. It does not get adequate oxygen and glucose supplies and according to Yaffe, “The metabolic syndrome is a risk factor for accelerated cognitive aging” (2007). The metabolic syndrome is composed of risk factors, meaning that one can reduce their risk by reversing this syndrome and getting healthy.

Healthy People 2020 has added a new section specifically on AD and dementia. The goal in 2020 for dementia including Alzheimer’s is to “reduce the morbidity and costs associated with, and maintain or enhance the quality of life for, persons with dementia, including Alzheimer’s disease” (Healthy People 2020). The objectives are to “increase the proportion of persons with diagnosed AD and other dementias, or their caregiver, who are aware of the diagnosis;” and to “reduce the proportion of preventable hospitalizations in persons with diagnosed AD and other dementias” (Healthy People 2020). Healthy People Document adding a section specifically for dementias is proof of the public health impact of this disease. It is important to keep research going and to make people aware of the efforts being put towards this disease.

### **Conclusion**

The prevalence of this disease is increasing, and without a cure, it is a major concern for many people as they age. The disease has been around for a very long time, but is only recently catching public health attention because so many people are living to older ages, where the risk of Alzheimer’s skyrockets. There are current therapies available to slow the progression of the disease, but nothing that will reverse the damage already done, and nothing yet that shows very substantial results. New diagnostic tools are becoming available that will allow those with AD to rule out other dementias, start the available treatments, and plan ahead for the later stages of the disease. The best way



to lower the risk for AD is to keep the whole body healthy, especially the heart and blood vessels, which fuel the brain with blood carrying oxygen and glucose. Exercise has no adverse side effects, it does not cost money, and it should be part of overall health habits everyday. Those who exercise regularly reduce their risks by avoiding the metabolic syndrome, and in doing so, keeping their brain working optimally. It is normal for the brain to accumulate some plaques and tangles as it ages, but it is not normal for these to completely kill off sections of the brain and cause such cell damage that daily life is severely altered. Since the exact reasoning behind the abundance of the plaques and tangles is unknown, it is best to do all that is possible to lower your risk factors for the disease and also to maintain high overall health. Since the disease is becoming so commonplace, education and awareness on ways to keep the brain healthy should become part of health education and regular doctor visits. A lot of research is going into the disease, and this will continue until all of the details are discovered. Treatments are getting better at slowing progression, and researchers are working their way towards prevention and hopefully a cure.

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