ABSTRACT

Alzheimer’s disease is a brain disorder that negatively affects memory and other cognitive abilities, including language and maintaining one’s orientation. Eventually, one’s ability to function cognitively or physically ceases altogether. The Mediterranean diet is characterized by large amounts of fruits, vegetables, olive oil, and a lack of red meat. Such a diet is most often consumed near areas surrounding the Mediterranean Sea and has been linked to a reduced risk of Alzheimer’s disease. This correlation is crucial to study as there is no current effective treatment for Alzheimer’s disease. Understanding what can prevent this disease is important for public health, in addition to helping to identify the causes of the disease, which aid in creating effective treatments in the future. In this paper, research on the link between the Mediterranean diet and the risk of developing Alzheimer’s disease as one ages will be examined. Evidence shows that people who follow the Mediterranean diet have a lower risk of Alzheimer’s as they grow older. Research indicates that this is due to the polyphenols in olive oil—a staple in the Mediterranean diet—and the general heart and body health that the diet promotes. This healthy diet also reduces obesity, which is linked to an increased risk of Alzheimer’s disease. In the future, more effort should be put into impeding the development of Alzheimer’s disease, which could potentially be done using knowledge of which populations are at risk, critical biomarkers of the disease, and preventative measures like the Mediterranean diet.

INTRODUCTION

Alzheimer’s disease is a brain disorder that negatively affects memory, other cognitive abilities such as language and orientation, and eventually the ability to function altogether. Alzheimer’s is the most common cause of dementia, which is the loss of cognitive function. When a person has Alzheimer’s disease, there is inflammation in the brain and abnormal deposits of proteins form tau tangles and amyloid plaques in the brain, causing neurons to die and brain tissue to shrink. These physiological effects begin to happen years before the person with the disease shows symptoms. Alzheimer’s disease is caused by a combination of genetic and environmental factors, but it is not clear exactly how they interact or how to predict whether or not someone will have Alzheimer’s when they are older (NIH, 2016). It is known that Alzheimer’s is linked to the apolipoprotein E ε4 (APOE ε4) allele. Alleles are alternate forms of a gene, which are found at the same place on a chromosome. One study showed that risk for Alzheimer’s disease increased from 20% to 90% in families with a history of Alzheimer’s disease. While the average age of Alzheimer’s onset was 68 in people with the allele, the average onset age in people without the allele was 84 (Corder et al., 1993). However, if one has the allele, they will not necessarily develop Alzheimer’s disease.

Alzheimer’s disease is important to study because there is currently no effective treatment for this condition. In 2017, 44 million people had Alzheimer’s or a related dementia disorder worldwide. It is the sixth leading cause of death in the United States, and the number of people with Alzheimer’s disease is only expected to rise in the future. By 2050, 16 million Americans are expected to be living with Alzheimer’s disease (Alzheimer’s Statistics, 2017). Thus, understanding this disease is crucial to finding prospective treatment options.

The Mediterranean diet is based on the typical cuisine of people in countries surrounding the Mediterranean Sea, including Italy, Greece, and Turkey. The diet mainly consists of foods from plants (fruits and vegetables) and carbohydrates (potatoes, beans, bread). Diet practitioners get most of their fat from olive oil and typically eat fresh fruit for dessert. Dairy, fish, poultry, and wine are consumed in small to moderate amounts, and the diet is low in saturated fats and red meat (Willett et al., 1995). The diet is associated with low obesity rates, and people from this region had some of the lowest rates of heart disease, certain cancers, and other diet-related diseases at the time of this literature review.

In a study on elderly people without dementia,
scientists observed which diet resulted in the lowest risk of Alzheimer's disease. The diet with the lowest incidence of Alzheimer's disease was "characterized by higher intakes of salad dressing, nuts, fish, tomatoes, poultry, cruciferous vegetables, fruits, and dark and green leafy vegetables and a lower intake of high-fat dairy products, red meat, organ meat, and butter" (Yian et al., 2010, 699-706). Such a description closely resembles the Mediterranean diet, suggesting that this diet reduces the risk of Alzheimer's disease.

Early research prompted scientists to investigate this relationship between Alzheimer's disease and the Mediterranean diet among a group of elderly people. Doctors studied 1,880 individuals, checking in with them every 1.5 years from 1992 to 2006 and measuring their adherence to a physical exercise regimen and Mediterranean diet. They discovered that groups of people who adhered only to regular physical activity or only to the Mediterranean diet both had lower incidence of Alzheimer's disease compared to people who did neither, and people who adhered to both physical activity and the Mediterranean diet had lower incidence of Alzheimer's disease than those who adhered to neither (Scarmeas et al., 2009). These results again indicate that following the Mediterranean diet reduces the risk of developing Alzheimer's disease.

The aim of this literature review is to discuss two of the mechanisms that explain how the Mediterranean diet might lower the risk of Alzheimer's disease: reducing obesity and increasing the intake of olive oil. Alzheimer's disease is very widespread, but discovering how to potentially prevent it furthers our understanding of the disease, so that one day we can devise methods of treatment and eradicate it altogether.

**POTENTIAL MECHANISMS TO PREVENT ALZHEIMER'S DISEASE THROUGH THE MEDITERRANEAN DIET: REDUCING OBESITY**

A significant method by which the Mediterranean diet reduces the risk of developing Alzheimer's disease is through decreasing rates of obesity. In a university teaching hospital, doctors studied people with and without Alzheimer's disease, discovering that people with Alzheimer's had a higher fasting glucose and lower insulin sensitivity than people without Alzheimer's (Meneilly & Hill, 1993). These results were corroborated by a more recent study which also found that higher fasting glucose levels in non-diabetic adults were associated with Alzheimer's disease. In addition, these higher glucose levels were only in the parts of the brain that Alzheimer's disease affects, further solidifying the connection between Alzheimer's disease and high glucose levels (Burns et al., 2013). Higher fasting glucose and low insulin sensitivity are characteristic of people who are overweight or obese (Akter et al., 2017). These results lend themselves to the hypothesis that obesity and Alzheimer's disease are linked; thus, preventing obesity could reduce the risk of developing Alzheimer's disease.

The connection between Alzheimer's disease and obesity is also demonstrated in a study done on mice, where mice with a genetic variant associated with Alzheimer's disease (APOE4) were discovered to be more likely to develop Alzheimer's disease if they were obese; mice were fed a diet high in fat and sugar to become obese. However, mice that had a version of the gene not linked to Alzheimer's disease (APOE3) did not develop the disease despite also being obese. Published in the journal eNeuro, the study also showed that obese mice had higher amounts of amyloid deposits which, as mentioned earlier, are the result of Alzheimer's disease (Moser & Pike, 2017). These results indicate that obesity alone does not cause Alzheimer's disease—one has to have the APOE4 allele to develop the disease. However, if an individual has this genetic variant they will not necessarily develop the disease. Following an unhealthy diet and contracting obesity increases the risk of developing Alzheimer's for those who are already susceptible. Since this study was conducted on mice, it is important to note that further research is needed to confirm the relationship between APOE4, obesity, and Alzheimer's disease in humans.

In a study on how genes interact with the environment, doctors studied people with normal body mass index (BMI), overweight BMI, and obese BMI, and each group included people with and without the apolipoprotein E4 allele (APOE e4). Likelihood of cognitive decline decreased with the presence of the APOE4 e4 allele if one had a normal BMI, suggesting that people who are overweight or obese have a higher likelihood of mental deterioration, especially if they have the allele (Kumar, Skarupski, Rasmussen, & Evans, 2014). This seemingly confirms that the relationship between cognitive decline and obesity found in mice also exists in humans. However, this study focused on general cognitive decline, not Alzheimer's disease specifically. Further research is needed to identify the correlation between the APOE e4 allele, obesity, and Alzheimer's disease in humans.

In a genetic study, single nucleotide polymorphisms (SNPs) associated with obesity or Alzheimer's disease were collected and compared. SNPs are differences in gene sequences of DNA (the carrier of genetic material) between people in which only one nucleotide (a unit of DNA) is changed. Thirty-one SNPs were associated with both an increased risk of obesity and Alzheimer's disease. The shared SNPs between Alzheimer's disease and obesity are linked to seven genes and ten biological pathways (Zhuang et al., 2017). Biological pathways are a series of reactions in a cell that lead to some product or change in said cell. This study demonstrates that obesity and Alzheimer's disease are linked since some of the same genetic material in humans is associated with both conditions. This evidence is in accordance with the
previously mentioned studies, which also suggest that Alzheimer’s disease and obesity are related. However, this study is more convincing, as it demonstrates a genetic link between the two conditions in humans, while other studies simply compared symptoms or were not specific to Alzheimer’s disease. Regardless, each of the aforementioned studies does connect obesity to Alzheimer’s disease, indicating that preventing obesity may reduce the risk of developing Alzheimer’s disease in old age.

**POTENTIAL MECHANISMS TO PREVENT ALZHEIMER’S DISEASE THROUGH THE MEDITERRANEAN DIET: OLIVE OIL**

Olive oil, particularly as a part of the Mediterranean diet, has been shown to prevent cognitive decline. In a randomized study, healthy patients at a high risk of cardiovascular disease were put into three groups: one control diet where participants were told to reduce dietary fat; and two on Mediterranean diet, one supplemented with additional nuts and another supplemented with additional olive oil. Both groups on the Mediterranean diet had significantly less cognitive decline, as measured over six years by the Wechsler Memory Scale, Color Trail Test, and Rey Auditory Verbal Learning Test, along with other assessments (Valls-Pedret et al., 2015). However, reduced rates of cognitive decline were also found in individuals that supplemented their diet with nuts, which casts suspicion on whether or not olive oil is the keystone component of the Mediterranean diet that prevents Alzheimer’s disease. Although cognitive decline is only a symptom and not a cause of Alzheimer’s disease, preliminary research linking olive oil with protecting against cognitive decline suggests more studies should be conducted on whether olive oil consumption prevents the onset of Alzheimer’s disease.

A promising study that solidifies this link investigated the phenols in olive oil: (3,4-dihydroxyphenyl)ethanol (DPE) and (p-hydroxyphenyl)ethanol (PE). By studying these phenols, doctors discovered that olive oil protected human cells, allowing them to continue being viable even after exposure to hydrogen peroxide or xanthine oxidase, both of which put oxidative stress on cells. In contrast, when the cells were not exposed to olive oil, they were unviable after exposure to hydrogen peroxide or xanthine oxidase. These results demonstrate the anti-oxidative properties of olive oil. The study concluded that phenols in olive oil could be used to protect against inflammatory diseases (Manna et al., 1997). Alzheimer’s disease is an inflammatory disease, so a high intake of olive oil, characteristic of the Mediterranean diet, could be beneficial in preventing Alzheimer’s disease.

Oleocanthal (OC), a phenol, is naturally found in extra virgin olive oil. A study of cells in vitro showed that treating synapses with OC resulted in less synaptic deterioration. Additionally, treated synapses did not attack amyloid beta-derived diffusible ligands (ADDLs), compounds that have possible therapeutic properties for Alzheimer’s disease (Pitt et al., 2009). Thus, research suggests that olive oil is beneficial for Alzheimer’s disease not only because it slows synapse deterioration, but also because it allows therapeutic compounds like ADDLs to enter the body that can help to treat the disease.

**FUTURE RESEARCH: BIOMARKERS AND INCREASED COMMUNICATION OF THE MEDITERRANEAN DIET**

While research on the Mediterranean diet has shown several promising correlations between the Mediterranean diet and a decrease in rates of Alzheimer’s disease no indication of how to effectively treat or diagnose the disease have been made. In the future, fighting Alzheimer’s disease could be spearheaded by further research into biomarkers, which will enable people to determine whether they have Alzheimer’s disease before symptoms develop, allowing them to begin treatment earlier. Furthermore, greater effort should be put into informing high risk populations, including women, African and Hispanic Americans, people with heart disease and/or diabetes, and people with a family history of Alzheimer’s disease, of the potentially protective nature of the Mediterranean diet (Alzheimer’s Statistics, 2017).

Biomarkers are measurable substances that indicate disease, infection, or environmental exposure. In the *JAMA Neurology* journal, a study shows that cerebrospinal fluid (CSF) beta-amyloid1-42 (Aβ42) can very accurately detect abnormal levels of Aβ deposition, which is a telltale sign of Alzheimer’s disease (Palmqvist et al., 2014). Thus, CSF is valuable for determining whether someone has Alzheimer’s disease before symptoms develop, making it viable as a biomarker. Biomarkers like CSF Aβ42 could be used in conjunction with current statistics of at-risk populations to determine which groups of people most need to be informed of the benefits of the Mediterranean diet.

**CONCLUSIONS**

Currently, the inverse relationship between the Mediterranean diet and Alzheimer’s disease is demonstrated through the Mediterranean diet’s reduction of obesity and the addition of the potentially healing phenols in olive oil, both of which have been independently linked to a lower incidence of Alzheimer’s disease. In addition, the Mediterranean diet as a whole has been connected to this same reduction of risk. As new research surfaces and we continue to expand our knowledge on what causes and potentially prevents Alzheimer’s disease, we can eventually understand how to treat it. For the immediate future, however,
efficiently preventing Alzheimer's disease should focus on populations most at risk, implementing the use of novel biomarkers to diagnose Alzheimer's disease before symptoms manifest, and spreading the word about preventative measures like the Mediterranean diet. While these suggestions are not permanent solutions, they could dramatically decrease the incidence of Alzheimer's disease—a step in the right direction.

REFERENCES
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About the Author

Fatima Mumtaza Tourk is a junior studying biomedical engineering. She works in Dr. Park's Assistive Robotics TeleMedicine laboratory, and is also the event management intern at the Reed Society for the Sacred Arts. She is a member of Alpha Omega Epsilon, a sorority for women in STEM, and is the Event Chair for the Muslim Students' Association. In addition, she is a graduate of the Women's Leadership Program and a member of Tau Beta Pi, an honors society for engineering. She hopes to fix problems in the healthcare industry with technological solutions.

Mentor Details

This paper was written with the mentorship of Dr. Carly Jordan.

Dr. Carly Jordan is an Assistant Professor of Biology, and the coordinator of the Science, Health, & Medicine Cohort in the Women's Leadership Program. She has a PhD in cellular biology from the University of Georgia, and her current scholarship focuses on science education, and exploring factors that encourage women to persist in STEM majors. In particular, she aims to understand if undergraduate programs like the Women's Leadership Program encourage students to pursue science careers after graduation.