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FOOD FOR THOUGHT

Researching nutrition's mitigating effects on the Pathogenesis of Alzheimer's Disease

CAROLINE COHEN

THIS PAPER DESCRIBES THE CONNECTION BETWEEN THE FOODS WE EAT AND OUR BRAIN HEALTH. IT ASSESSES THE EFFECTS OF CERTAIN NUTRIENT GROUPS ON THE BRAIN AND THEIR ROLE IN THE PATHOGENESIS OF ALZHEIMER'S DISEASE (AD), SPECIFICALLY THE BRAIN ABNORMALITIES ASSOCIATED WITH IT, INCLUDING TAU TANGLES, AMYLOID-BETA PLAQUES, AND OXIDATIVE STRESS. THE INTAKE OF A HIGH FAT DIET, WITH SATURATED FATS IN PARTICULAR, HAS BEEN SHOWN TO AGGRAVATE BETA-AMYLOID PROTEIN ACCUMULATION AND THE FORMATION OF TAU TANGLES, WHEREAS A DIET LOW IN SATURATED FAT AND HIGH IN N-3 FATTY ACIDS HAS BEEN SHOWN TO REDUCE AMYLOID-BETA PLAQUE FORMATION AND LESSEN COGNITIVE DECLINE. AN ANTIOXIDANT-RICH DIET IMPROVES LEARNING AND MEMORY IN MICE AND COMBATS THE HEIGHTENED OXIDATIVE STRESS FOUND IN AD BRAINS. THE MIND AND DASH DIETS HAVE BOTH BEEN SHOWN TO DIMINISH ALZHEIMER'S INCIDENCES, BUT THE MIND DIET PROVES ITSELF TO BE MORE IMPACTFUL THAN THE DASH DUE TO ITS SPECIFIC EMPHASIS ON THE CONSUMPTION OF FOODS HIGH IN ANTIOXIDANTS.

NUTRITION'S DETERMINATION OF OVERALL HEALTH

Food has effects on your body and overall health that may not be completely obvious from the outside. Many people believe that regardless of food choices, having a smaller body frame means being healthy. However, nutrition research has shown that certain nutrient groups have various effects on the body, including the brain, that prevent or promote the development of diseases and other health problems. Following a nutrient-specific diet plan over one's lifespan can serve as a preventative measure for the development of Alzheimer's disease (AD). Numerous studies suggest that guided consumption of vitamin C, vitamin E, antioxidants, and essential fatty acids can mitigate the progression of amyloid-beta plaques, tau tangles, and oxidative stress, thus constituting a preventative and therapeutic, non-pharmaceutical approach to tackling AD.

ALZHEIMER'S RISK FACTORS AND COMMON BRAIN ABNORMALITIES

The hallmark brain markers found in AD patients are primarily tau tangles and amyloid-beta plaques. The presence of both of these lead to the impairment of memory that characterizes the illness. The accumulation of beta-amyloid protein forms these plaques and triggers both synaptic and memory loss, therefore facilitating AD development (Nakandakari et al., 2019). Tau tangles are composed of aggregated tau proteins that interfere with cellular mechanisms, ultimately causing the cell to die (ibid). The diminishing size of the brain is a result of neuronal and synaptic death, which are more strongly correlated with the memory loss in AD than beta-amyloid plaques and tau tangles (Samadi et al., 2019). Slowing the progression of plaques and tangles would elicit cessation, or at least slowing, of the development of the illness and is something that nutrition can feasibly do.

In addition to these precursors, obesity is a main risk factor for AD (Szczechowiak et al., 2019). This is widely unknown, for it is not typically mentioned among the commonly known health risks associated with obesity such as diabetes, hypertension, and atherosclerosis. Given the rising rate of obesity today, the associated risk of Alzheimer's with obesity should be made known to the public. The current lack of awareness stems directly from the common disassociation made by consumers between what they eat and their health beyond body weight. Food is meant to nourish and fuel the body, but when food choices are made ignorantly, they may lead to unexpected risks.

FAT CONSUMPTION AGGRAVATES BETA-AMYLOID PROTEIN ACCUMULATION AND FORMATION OF TAU TANGLES

High fat consumption has been shown to exaggerate beta-amyloid and tau protein aggregation. Nakandakari et al., 2019 conducted a study in which mice were given either standard chow or a short-term high-fat diet to assess the effects of a high-fat diet on the AD precursors. It was shown that consumption of the high-fat diet increased beta amyloid content and tau phosphorylation, which leads to tau tangles and neuronal death. The high fat diet was shown to trigger apoptotic alterations in the hippocampus, thus catalyzing the diminishing size of the hippocampus in AD.

Next, the researchers looked specifically at the impact of saturated fats, which are believed to be the most unhealthy and are recommended to be consumed in moderation. They directly applied palmitate, a component of saturated fatty acids, to neurons and microglial cells over a ten-day period. Direct application of palmitate increased beta-amyloid and tau protein content. These results suggest that diets in saturated fat, amplify the production of beta-amyloid plaques and tau tangles. Saturated fat is therefore a nutrient that should be consumed sparingly due to its neurodegenerative effects (Nakandakari et al., 2019).

“The diminishing size of the brain is a result of neuronal and synaptic death, which are more strongly correlated with the memory loss in AD than beta-amyloid plaques and tau tangles.”

Another study conducted by Theriault et al. in 2016 replicated these results with mice being fed a high-fat diet containing high levels of saturated fatty acids for four months. It was found that the mice given this high-fat diet showed increased amyloid-beta content in cerebral microvasculature compared to control animals (Theriault et al., 2016). These results support the hypothesis that a high-fat diet exacerbates the development of AD.

POSITIVE EFFECTS OF A DIET LOW IN SATURATED FAT: THE MIND DIET

The Mediterranean-DASH Intervention for Neurodegenerative Delay (MIND) diet focuses on the consumption of plant-based foods and fish to limit the intake of animal food sources and saturated fats. This diet is a hybrid between the Mediterranean diet and the Dietary Approaches to Stop Hypertension (DASH) diet, created with the goal of improving brain health. The MIND and DASH diets are compared later in this paper to examine the varying effectiveness of each due to a key difference in foods incorporated. Following the guidelines of the MIND diet has been shown to slow the development of the typical precursors of AD. When studied in mice, it was found that high intake of n-3 fatty acids from fish sources had the opposite effects of saturated fat. N-3 fat consumption was found to decrease beta-amyloid formation and oxidative stress and increase synaptic proteins and dendritic spine density (Berendsen et al., 2018 as reviewed by Samadi et al., 2019). This increase in synaptic proteins and dendritic spine density serves as a preventative mechanism from AD symptoms, given that losses in these entities have the greatest association with the memory impairments seen in AD.

The n-3 fatty acids found in fish typically include omega-3, docosahexaenoic acid (DHA), and eicosapentaenoic acid (EHA) (Vauzour et al., 2015 as reviewed by Szczechowiak et al., 2019). All of these components have been shown to improve neuronal transmission and regulate the excitability of neuronal membranes, thus improving memory and learning in healthy, non-AD individuals (ibid). Additionally, it has been found that these n-3 fatty acids can promote immunity in patients who have been diagnosed with mild

cognitive impairment and have therefore not yet progressed to the level of decline that would constitute their impairment as AD. This immunity refers to n-3 fatty acids promoting the phagocytosis of amyloid-beta proteins, therefore dissolving plaque aggregation and reducing memory loss symptoms (Fiala et al., 2017 as reviewed by Szczechowiak et al., 2019).

An additional study conducted by Schaefer et al. in 2006 reported these same results of further deteriorating memory. Elderly people were given a questionnaire regarding their fish intake habits and were then placed into quartiles based on their levels of consumption of fish that is high in DHA. Those found to consume the most DHA-containing fish had a 47% lower risk of dementia relative to those in the bottom three quartiles (Schaefer et al., 2006). This further demonstrates that DHA consumption in fish is correlated with lower risk of cognitive decline.

THE MIND DIET IS EASIER TO FOLLOW AND MORE EFFECTIVE THAN DASH

A well-balanced diet is one that naturally contains all of the vital nutrients without the need for supplementation. An example of a diet within this category is the DASH diet, which emphasizes the consumption of non-processed, plant-based foods and limits the intake of animal products and other foods high in saturated fat (Samadi et al., 2019). Studies of this diet in elderly people show that subjects who followed the diet the most strictly and received high DASH diet scores, were seen to have a 39% reduction in Alzheimer's incidence compared to those who received the lowest DASH diet scores (Morris et al., 2015). Evidently, following a healthful, plant-based diet has the ability to lower the risk of Alzheimer's development considerably.

One study conducted by Morris et al. in 2015 observed that those following the MIND diet had an even greater preventative effect on Alzheimer's incidence than did those following DASH. The DASH and MIND diets focus on the same target and avoidance foods, but the MIND diet specifically incorporates berries and green leafy vegetables. As a result of this addition, MIND diet consumers were

“...the mice given this high-fat diet showed increased amyloid-beta content in cerebral microvasculature compared to control animals.”

shown to have slower cognitive decline than DASH consumers. Those who complied most strongly to the MIND diet and fell into the top tertile of MIND diet scores had a 53% reduction in the incidence of AD, compared to those who fell in the lowest tertile of MIND diet scores. Those who fell in the middle tertile of MIND diet scores still had a 35% reduction in the rate of AD development. Even low compliance showed significant results, similar to those with the greatest compliance to DASH. This indicates that the DASH diet must be followed strictly to achieve the same results as a loose following of the MIND diet (Morris et al., 2015).

It is important to note that the DASH diet's guidelines are far more demanding than those of the MIND, and yet the MIND diet is more powerful even at low compliance. To achieve a high MIND diet score, consumption includes only two servings of vegetables per day, two servings of berries per week, and only one serving of fish per week (Morris et al., 2015). In contrast, a high DASH diet score requires three to four servings of fruits and three to four servings of vegetables per day, in addition to six or more servings of fish per week (ibid). The MIND diet is far easier to follow and results in greater protection against AD. So what is it that makes the addition of blueberries and green leafy vegetables so significant? This answer lies within the high antioxidant content of these additions compared to other fruits and vegetable choices that may be made in the DASH diet due to no specification.

ANTIOXIDANT TREATMENT IMPROVED LEARNING AND MEMORY IN MICE

Oxidative stress refers to a damaging interaction between reactive oxygen species (ROS) and vital compounds in their surroundings in the brain that are associated with the amyloid beta plaque and tau tangle precursors (Huang et al., 2016). Oxidative stress is caused by an imbalance between antioxidants and oxidants, which occurs due to either decreased antioxidant defense or increased free radical concentration. Free radicals contain at least one unpaired electron in their valence shell, which comes from the reduction of the oxygen in water. This reduction reac-

tion creates strongly reactive hydroxyl radicals, which are a type of ROS. These reactive hydroxyl radicals react with fats, proteins, nucleic acids, and other molecules and alter their functions and structures. Oxidative stress occurs when ROS molecules are created in excess concentrations, thus creating the imbalance between antioxidants and oxidants. Antioxidants serve to prevent the formation of ROS and are therefore an important component in protecting the brain (ibid). Cells in the body typically contain antioxidant defense mechanisms to protect against oxidative stress on their own, but it has been found that AD patients have low levels of these anti-oxidative molecules in their cells (Ansari et al., 2010 as reviewed by Thapa et al., 2017). This suggests that these low levels of endogenous antioxidants may contribute to the ROS overload that produces oxidative stress in AD patients. This endogenous anti-oxidative mechanism diminishes with age, therefore putting elderly people at a greater risk for developing AD (ibid). This demonstrates the importance for the elderly population and those knowingly at risk of AD to consume antioxidants through food sources.

Studies have tested the effects on oxidative stress of distributing the antioxidant ascorbic acid to mice, where it was shown that ascorbic acid and vitamin E treatment promoted facilitatory effects on memory retrieval and learning (Shahidi et al., 2008 as reviewed by De Oliveira et al., 2019). High levels of anxiety have been proven to impair learning capabilities and memory. The ascorbic acid given to the mice served to decrease oxidative stress and lower their anxiety levels, thus increasing their ability to both learn and draw from their memories (Hasanein et al., 2010 as reviewed by De Oliveira et al., 2019). The second portion of the study gave vitamin E in addition to the ascorbic acid to diabetic mice, in whom they found both improved memory and reversal of memory deficits (ibid). This addition of antioxidants in both groups served to diminish oxidative stress by reestablishing the balance between oxidants and antioxidants in the brain, thus mitigating the problems of memory loss seen that result from oxidative stress. It can therefore be concluded that consuming foods rich in antioxidants have the ability to reduce oxidative stress and improve deficits in learning and

“...the DASH diet's guidelines are far more demanding than those of the MIND, and yet the MIND diet is more powerful even at low compliance.”

memory seen in AD and could thereby be used as a potential therapeutic or prevention mechanism for the disease.

THE MIND DIET IS MORE EFFECTIVE THAN DASH DUE TO ITS EMPHASIS ON ANTIOXIDANT INTAKE THROUGH BERRIES AND LEAFY GREEN VEGETABLES

The MIND specifically incorporates berries as a guideline for its fruit intake, which contain higher levels of antioxidants than other fruits. A study conducted by Joseph et al. in 1999 shows the power of berries in mitigating oxidative stress which explains the heightened effectiveness of the MIND diet over the DASH, which does not specify berry consumption. The study was done on adult rats to determine the effects of both blueberry and strawberry consumption on brain health. Rats were given blueberry or strawberry extract in their water for eight weeks. After the eight week period, the effects on oxidative stress were measured based on the production of ROS in the rats' brain tissues. Results showed that the rats that consumed strawberries and blueberries showed greater oxidative stress protection than the rats in the control group, with the blueberry group showing slightly higher protection than the strawberry group (Joseph et al., 1999). Blueberry extract has been shown to reduce oxidative stress in the brain by increasing the synthesis of glutathione, which is an antioxidant (Brewer et al., 2010 as reviewed by Subash

et al., 2014). Berries contain higher antioxidant content than most other fruits, which is why they are added to the criteria of the MIND diet and is ultimately what makes it more successful in reducing the risk of Alzheimer's. While the research on the effects of green leafy vegetables on the brain is inconclusive, it can be speculated that due to their high vitamin E content, their impact is the same as was shown in the study conducted by De Oliveira et al. in 2019.

CONCLUSION

Figure 1 shows the relationship between eating a healthy diet and having a healthy brain. In this context, a healthy diet is classified as a high intake of antioxidants and n-3 fatty acids, and an unhealthy diet consists of high consumption of saturated fats, trans fats, and simple carbohydrates. As has been outlined in this paper, the nutrients in the healthy diet decrease oxidative stress, thereby decreasing amyloid-beta plaque and tau tangle formation, thus mitigating the effects of AD. In contrast, consuming the nutrients within the unhealthy diet produces the opposite effects in each component. These effects serve to deem a healthy diet as a neuroprotective mechanism, and an unhealthy diet a neurodegenerative mechanism.

Nutrition is a non-pharmaceutical approach to decrease risk against AD, which is a highly feasible and easily

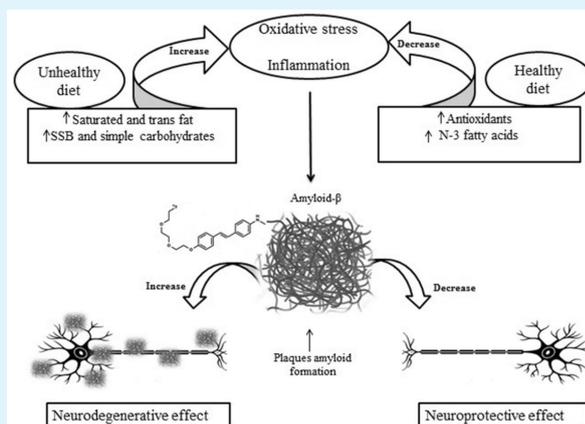
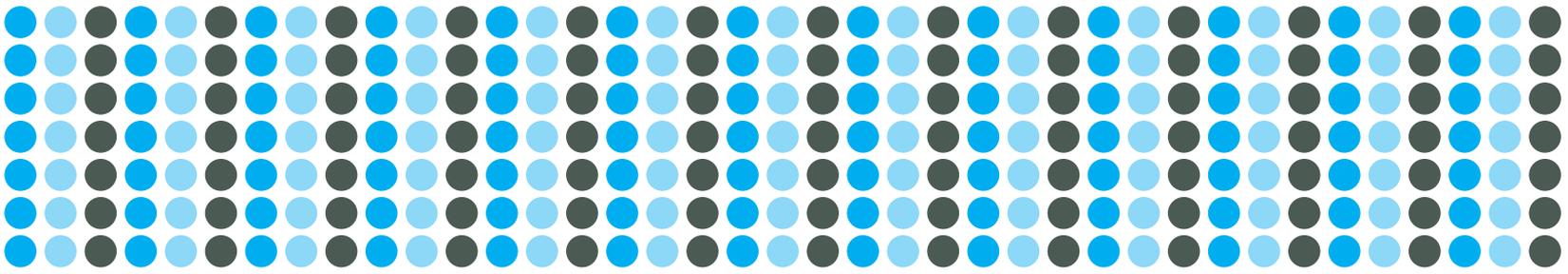


FIGURE 1: DEPICTS THE INFLUENCE OF VARIOUS NUTRIENT GROUPS ON FACTORS THAT PLAY A ROLE IN THE PATHOGENESIS OF ALZHEIMER'S. IT DEMONSTRATES TWO SPECTRUMS OF NUTRITION DECLARED AS HEALTHY VERSUS UNHEALTHY AND WHETHER THEIR NUTRIENTS HAVE BEEN SHOWN TO ADMIT NEUROPROTECTIVE EFFECTS OR NEURODEGENERATIVE EFFECTS, RESPECTIVELY. THIS GRAPHIC LAYS OUT THE DIRECT CONNECTION BETWEEN DIET AND BRAIN HEALTH THAT CAN PROTECT FROM OR CONTRIBUTE TO THE DEGENERATION OF THE BRAIN IN ALZHEIMER'S DISEASE. (FROM SAMADI ET. AL)

controllable factor that individuals can take upon themselves with minimal effort. Given the little knowledge of the average person about the connection between the foods they eat and their brain health, the government should distribute a public service announcement to promote the importance of nutrition and how it can impact not just your weight and your heart, but also the brain. There are many claims about other nutrient groups, such as foods high in zinc and aluminum, however the evidence found is limited. With the current research available, it is difficult to deduce the details to make a nutritional approach concretely effective. These gray areas include the duration of time this dietary approach needs to be followed for it to be effective, as well as how strictly. While one may argue that there are too many alternative factors involved to report a connection between food and the brain, with the few therapies available for Alzheimer's currently, any step toward a potential cure should be considered. We ought to take advantage of such scientific findings and promote more informed consumption as a society to increase longevity and influence the factors that contribute to chronic illness where we can.

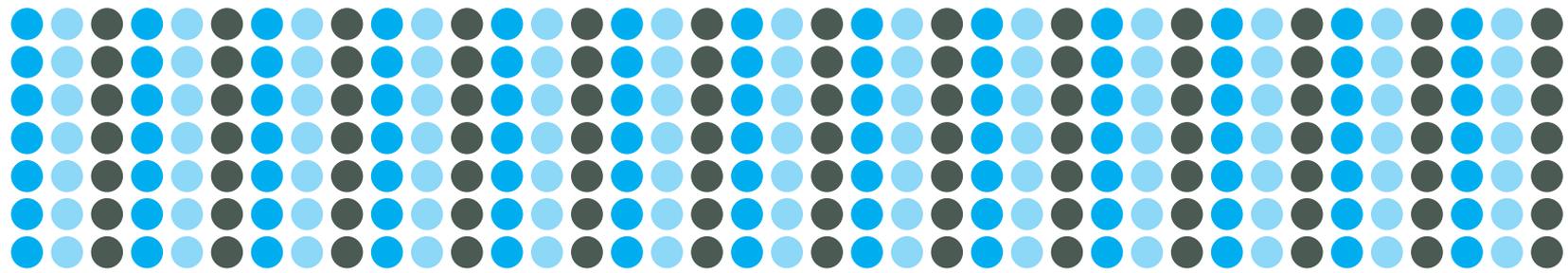
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- 15 EASTER PROCLAMATION OF 1916**
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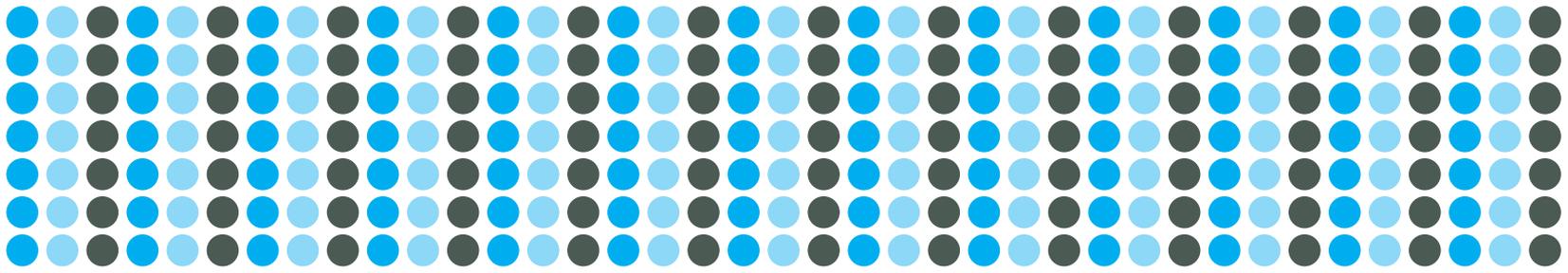
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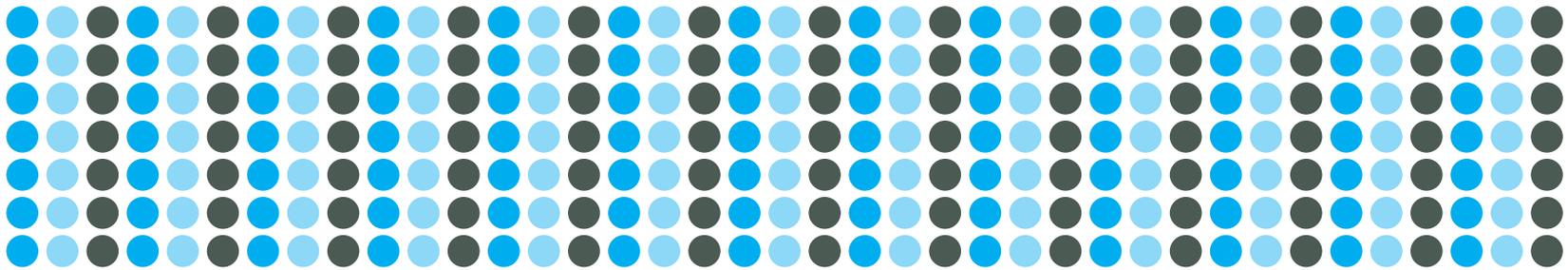
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