**Current Status of Research on Risk Reduction and Treatments for Alzheimer’s Disease (AD)**

**Robert Harrison Black, Osher Life Long Learning Institute, University of North Florida. Jacksonville, Florida, USA.**

**e-mail** **bob@life401.com**

**Abstract:**

When Dr. Alzheimer documented the loss of cognition in his 44-year-old patient, the condition was rare. It has since become a pandemic. The condition causes the brain to be unable to use glucose for fuel, and brain cells die. By the final stages of AD, this process—called brain atrophy—is widespread, causing significant brain volume loss. Lifestyle studies research have found factors that reduce the chance of contracting AD. These lifestyle factors match those recommended to prevent cardiovascular and other diseases. Both gingivitis and E. coli bacteria have been implicated in AD. These bacteria may be more a symptom than a cause. In studies, healthy brains had some gingivitis and E. coli bacteria. Added sugar consumption and unsaturated fatty acid consumption correlate with increased AD. There are biochemically studies that show these increases may be the cause.

The principal ketones (also called ketone bodies), β-hydroxybutyrate and acetoacetate, are the brain’s primary physiological alternative fuel to glucose. These brain ketones are as useful to the brain as glucose. These ketone bodies become available when in ketosis and positively affect cognition. Mental and physical exercises have a modest impact on AD symptoms but do not stop the decline in cognition. AD patients given physical and mental exercises could no longer care for themselves or function independently. Several drugs have been developed to reduce AD symptoms but do not prevent the decline in cognition. Two drugs have been approved to prevent the formation of ß amyloid placks. These drugs only slightly slow cognitive decline and only work in the early stages of AD. Alves et al. revealed the potential for anti- β Amuloid therapies to compromise long-term brain health by accelerating brain atrophy. [48]

Only glucose replacement with ketone bodies has been shown to stop and potentially reverse AD. This approach needs long-duration, double-blind clinical studies to prove effectiveness.

**Key words:**

Alzheimer’s drugs, β-hydroxybutyrate, and acetoacetate for brain energy, gingivitis and E. coli bacteria, omega-6 fatty acids causing inflammation, ketogenic diet for Alzheimer’s, amyloid and tau protein deposits

**1.0 Introduction:**

AD is named after Dr. Alois Alzheimer. In 1906, Dr. Alzheimer documented changes in the brain tissue of a woman who had died at age 55 of a rare mental illness. In AD, as neurons are injured and die throughout the brain, connections between networks of neurons may break down, and many brain regions begin to shrink. ß Amyloid placks and tau tangles form in place of dead brain cells. [47] There is also agreement in the literature that brain glucose uptake is impaired. By the final stages of AD, this process—called brain atrophy—is widespread, causing significant brain volume loss. [23] New brain cell formation does not appear sufficient to halt or reverse this decline. [25]

The author sought to answer these questions: (1) Can neuron death be halted or reversed? (2) Can the problem with the brain’s use of glucose be mitigated? (3) Can cognitive decline be prevented? 4) Can new neurons be grown?

Despite billions spent to find effective risk reduction recommendations or treatments for AD, AD has become a pandemic. The recommendations for AD risk reduction match those for reducing the likelihood of cancer, heart disease, and other noninfectious diseases. Following the onset of AD, none of these recommendations are effective. Drugs developed to reduce AD symptoms do not appear to stop or even slow the death of neurons. These drugs help communication and do reduce the burden on caregivers. No medications have been proven to halt the progress of neuron death. The FDA has approved two drugs to slow the disease’s progression. The clinical data was mixed on the effectiveness of both, and the scientific panel that reviewed the first drug recommended disapproval.

1. **Lifestyle:**

2.1 Livingston, writing in Lancet, said less education, hypertension, hearing impairment, smoking, obesity, depression, physical inactivity, diabetes, low social contact, excessive alcohol consumption, traumatic brain injury, and air pollution account for around 40% of worldwide dementias. These dementias could theoretically be prevented or delayed by mitigation of these factors. [14]

These items on Livingston’s list match recommendations for a healthy heart and a lower cancer risk. These recommendations and those from Baumgart (below) will increase the likelihood of a better life; everyone should follow these recommendations. While these recommendations show how to reduce AD risk, they do not show how to stop or reverse AD progression.

|  |  |
| --- | --- |
| Evidence strength | Factors |
| Strong evidence of increasing risk | Traumatic brain injuryMid-life obesityMid-life hypertensionCurrent smokingDiabetes |
| Lower evidence of increased risk | History of depressionSleep disturbances |
| Unclear evidence of increased risk | Hyperlipidemia |
| Strong evidence of decreased risk | Years of formal educationPhysical activity |
| Moderate evidence of decreased risk | Mediterranean diet (discussed later)Cognitive training |
| Lower evidence of decreased risk | Moderate alcohol consumption |
| Unclear evidence of decreased risk | Social engagement |

Table 1. Baumgart Cognitive decline risk factors for AD. [3]

The above chart by Baumgart outlines the risk factors for AD and other dementias. Many clinical studies describe the Mediterranean diet. They are not consistent, but they have two things in common. They are low in added sugars and use olive oil, not inflammatory vegetable oils like soybean. [3] Appendix A explains why the term Mediterranean Diet is not useful. Appendix B provides a clear description of a diet to combat AD.

**2.2** Chatterjee et al. discovered a link between diabetes and AD. This link supports the importance of sugar as a cause of AD. [6]

**2.2** Melzer et al. stress the need for micronutrients such as vitamins and minerals to maintain health. They also recommend optimizing macronutrients. This recommendation was not further developed. They assert nutritional status as the most critical modifiable factor regulating the gut microbiota at different time points across the lifespan and under various health conditions. Metzeler identified the brain-gut link as essential. [20]

**2.3** Both gingivitis and E. coli bacteria have been implicated in AD. Of course, AD patients forget to brush their teeth. Both of these bacteria live on dead tissue. The dead brain cells provide nourishment for these bacteria. [1] [38] Zahn has noted the fibers in E. coli and their similarity to those in AD. These bacteria may be more a symptom than a cause. In both studies, healthy brains had some gingivitis and E. coli bacteria.

**2.4** Sugar consumption**:**

AD increase correlates with increased added sugars; these include sucrose, high fructose corn syrup, maple syrup, agave, honey, and others. The average American ate only 2 pounds of added sugar a year two hundred years ago. [22]

|  |  |
| --- | --- |
| Year |  Consumption  |
| 1814 | 2 |
| 1970 | 123 |
| 2014 | 152 |

Table 2. Added sugar consumption in pounds per year. [22]

In one year, we now consume about 152 pounds of added sugar or nearly 3 pounds per week. Increased sugar consumption is linked to AD. Both correlation and biochemistry show this link.

Seneff et al. described the detrimental effects of a high carbohydrate diet. [33]

The principal ketones (also called ketone bodies), β-hydroxybutyrate and acetoacetate, are the brain’s primary physiological alternative fuel to glucose. These two of many studies in mild-to-moderate AD have shown that these brain ketones are as useful to the brain as glucose in healthy age-matched controls. [7], [10] Published clinical trials demonstrate that increasing ketone availability to the brain via moderate nutritional ketosis with medium-chain triglyceride oil has a beneficial effect on cognitive outcomes in mild-to-moderate AD and mild cognitive impairment. [10]

**2.5** Dietary Fats:

Large quantities of omega-6 seed oils are now being consumed. These oils cause inflammation that damages all tissue, including the heart, brain, kidneys, and pituitary.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Oil type | 1914 | 1909 | 1999 | Percent change 1909-1999 |
| Soybean | 0 | .01 | 11.6 | 116,300 |
| Canola 1 | 0 | .01 | 0.8 | 16,700 |
| Safflower | 0 | .04 | .05 | 25 |
| Cottonseed | 0 | .4 | .31 | -21 |

Table 3. Consumption of omega-6 oils in Kilograms per person per year. [42]

Omega 6 oil consumption has also tracked AD. Something changes in the brain from being able to use glucose for fuel to needing β-hydroxybutyrate and acetoacetate. The cause of this change in brain metabolism has not been found. Double-blind and biochemical studies are required to know what these oils do to us.

In addition, omega-6 fats are unsaturated and more likely to become oxidized in LDL cholesterol. These oxidized LDL particles cannot be used in cells and will continue circulating, causing systemic inflammation. Oxidized LDL will also stick to the walls of the arteries causing plaques. Fats sticking to the walls of arteries causes a cascade of events that lead to clots. This cascade consists of continued accumulation of fatty deposits, attempts by white blood cells to clear the oxidized LDL from the arterial walls, inflammation signals from the white cells, inflammation of the blood vessels that have the deposits, and finally, the buildup of deposits and the formation of clots. Ravnskov and Kromer focused on heart disease, but the findings may also apply to the even finer capillaries in the brain.[29],[12]

Omega 3 fatty acids, primarily from fish, have been shown to reduce the probability of AD [16]. Olive oil is low in omega-6 fatty acids, which may be why some Mediterranean diets show positive results.

**2.6** Ketogenic Studies**:**

A high-fat ketogenic diet can achieve nutritional ketosis by providing 20–70 g/day of medium-chain triglycerides containing the eight- and ten-carbon fatty acids octanoate and decanoate or by ketone esters. [32] Insulin blocks the metabolism of fats and promotes the storage of body fat. To use eight- and ten-carbon fatty acids, octanoate, and decanoate, carbohydrates must be limited. Given the acute dependence of the brain on its energy supply, it seems reasonable that the development of therapeutic strategies aimed at AD must target how the underlying problem of deteriorating brain fuel supply can be corrected or delayed.

There are many patients on a ketogenic diet to prevent seizures. The ketogenic diet is high in fat, adequate in protein, and very low in carbohydrates. A typical ketogenic diet for controlling seizures consists of 70% to 80% fats, 20% proteins, and 5% to 10% carbohydrates. Doctors typically recommend the keto diet to treat epilepsy in children of all ages, including infants. Adults usually do not prefer ketogenic diets because the limited food choices make the diet hard to maintain. The keto diet has also been used in other neurological conditions, including AD and an autism spectrum disorder. [5]

Taylor et al. found that AD could be reversed using medium-chain triglycerides and a ketogenic diet. Their trial only succeeded with subjects with very mild or mild cognitive impairment. With the more severely cognitively impaired, the dropout rate was 100%. These studies have a problem with the subject’s unwillingness to stay on the diet or the heavy caregiver burden being too difficult.[35]

Melzer et al. recognized the loss of the ability of the brain to use glucose and the effectiveness of medium-chain triglycerides in the pathology of AD. This revelation was not further developed. [20]

Coconut oil is high in medium-chain fatty acids, easily converted to beta-hydroxybutyrate and acetoacetate; our brain can use these instead of glucose. Many studies have been done on both coconut oil and medium-chain triglyceride oil. I reference one by W M A D B Fernando. [9] All of the studies with medium-chain triglyceride oil show positive results. Most studies with coconut oil studies show positive results.

The study by Xu et al. showed a significant (p < 0.01) reduction in the AD assessment scale scores used by Xu. There was a 2.62 improvement for the medium-chain triglyceride oil. And a 2.57 worse score for the placebo over 30 days. They used medium-chain triglycerides (MCT) oil with canola oil as a control. The TC, HDL-C, β-hydroxybutyrate, and acetoacetate concentrations were significantly higher in the MCT group than in the placebo group. [37]

Roy et al. used multimodal imaging to show that a ketogenic intervention in mild cognitive impairment improved the dorsal attention network’s functional, metabolic and structural integrity. This network enables us to interact with the environment. The 6-month ketogenic medium chain triglyceride supplementation increased functional connectivity within the dorsal attention network as a direct function of improved brain energy status due to higher ketone availability. Attention also improved as a function of enhanced functional connectivity. Analysis of the comprehensive structural map of neural connections in the brain revealed increased fiber density within the dorsal attention network following ketogenic medium-chain triglyceride consumption. [31]

Rebello et al. “Consumption of 56 g/day of medium chain triglycerides for 24 weeks increases serum ketone concentrations and appears to be a candidate for larger randomized control trials in the future that quantify the modulation of cognitive function through supplementation with ketone precursors in patients with mild cognitive mild impairment.” [27]

Poorni Sandupama recommends Coconut oil as a treatment for AD in the Journal of Future Foods review. [41]

Kane et al. have done a compensative study of attempts to cure AD. Some of the studies provided temporary symptom relief, but none prevented the progress of the disease. “We found mostly low-strength evidence that a wide variety of interventions had little to no benefit for preventing or delaying age-related cognitive decline.” [11] A ketogenic and medium-chain triglyceride diet was not on the list of treatments studied by Kane et al..

**2.7** The Indian spice curcumin is a principal constituent of the spice turmeric. Recent research on amyloid-β and curcumin has revealed that curcumin prevents amyloid-β aggregation and crosses the blood-brain barrier (BBB), reaches brain cells, and protects neurons from various toxic insults of aging and amyloid-β in humans.” [28] Molecular variations of curcumin may also be effective against AD.

**2.8** Salt: “There is evidence that high salt intake is associated with poor cognition. However, findings are mixed due to poor methodological quality and the studies’ heterogeneous dietary, analytical, and cognitive assessment methods and design. Reduced sodium intake may be a potential target for intervention. High-quality prospective studies and clinical trials are needed.” [21]

O’Donnell found that a salt intake between 3 and 6 grams per day was associated with a lower risk of death. The lowest level of AD was when consuming salt to taste. This level of salt intake is between 3 to 5 grams per day. Low salt may be part of the problem. [26] No double-blind clinical studies on salt and AD were found.

**2.9** Mental exercise

Woods et al. found that mental exercises have a minimal long-term effect in preventing a decline in cognitive function. The researchers found that mental stimulation improved memory and thinking test scores for those with dementia, equivalent to a six to nine-month delay in worsening symptoms. Some studies found dementia patients who engaged in such activities had increased feelings of well-being and a better quality of life, including improved communication and interactions with those around them. They were, however, no better able to care for themselves or function independently. [36]

**2.10** Physical exercise

Chen et al. Studied exercise as a treatment for AD. The trials included people in the mild to moderate stages of dementia, and the intervention did not appear appropriate for people with severe dementia. No evidence was found of improvements in participants’ mood or ability to care for themselves or function independently. There was no reduction in behavior found difficult by staff or caregivers. Family caregivers, including those trained to deliver the intervention, did not report increased levels of strain or burden.[43]

Earlier work by Rolland showed the same effect [30]

**2.11** Psychological factors

Sonja Sulkava et al. described the association between psychological distress and incident dementia. This important link needs to be pursued but is beyond this paper’s scope. [39]

**3.0 Drugs for AD:**

Drugs have not been shown to reverse AD. The recently approved drug Aducanumab is one in a long line of failed drugs that prevent or reduce amyloid beta plaques. Trials of Aducanumab have shown mixed results. It will likely fail because the prevention of amyloid beta has consistently failed to delay or reverse AD. Other drugs stimulate the brain and temporarily show delay or reversal. None have been shown to delay or reverse brain cell death in AD.

Tampi, Forester, & Agronin also reviewed the clinical trials of Aducanumab. They did not find evidence of a long-term benefit from Aducanumab. They showed why the Drugs Advisory Committee of the FDA voted, with ten members against it and one member uncertain that it was not reasonable to consider the evidence of clinical benefit from Study 302 as primary evidence of the effectiveness of aducanumab. [34]

van Dyck et al. studied Lecanemab in early AD. It was approved for early-stage AD. It is one in a long line of beta-amyloid prevention drugs. If beta-amyloid is scar tissue and not the cause, it will join the long list of minimally effective drugs. That is not a long-term solution. [44]

Until recently, in the United States, only five treatments were approved by the US FDA for neurocognitive symptoms of AD. These include three cholinesterase inhibitors (donepezil, galantamine, and rivastigmine), one N-methyl-D-aspartate receptor antagonist (memantine), and a combination of donepezil and rivastigmine. The first four drugs are also licensed in the European Union. In the United States, a fixed-dose combination of donepezil and memantine was approved in 2014 for treating individuals with moderate to severe AD dementia who are stable on donepezil. These drugs reduce symptoms but do not slow the progression of AD. [34]

Mehta et al. studied the failure of AD drugs. The article was titled “Why do trials for AD drugs keep failing?” They reviewed drugs that were anti-amyloid monoclonal antibodies, used gamma-secretase to decrease the production of amyloid, controlled tau protein, enhanced neurochemicals, and blocked antihistamines. All were failures. [18]

**4.0 Conclusion:**

Lifestyle

Our increasingly sedentary lifestyle is likely a cause of a portion of the increase. Intellectual stimulation has been shown to slow the development of AD symptoms. By delaying the diagnosis, some people who would have been diagnosed with AD may die of other causes before diagnosis.

Added sugars that contain fructose and omega-6 seed oil consumption have increased exponentially. This increase has matched the growth of AD. It is not in the best interest of pharmaceutical companies to research lifestyle factors that may halt or even reverse AD progression; it is also not in the best interest of food companies to find that fructose and omega-6 oils are the cause. Because of funding, the lifestyle studies of the fructose and omega-6 seed oil hypothesis have used fewer subjects and have been short-duration. Omega 6 oils are linked to AD. Both correlation and biochemistry show this link. We do not have a way to determine the percentage is caused by sugar and what percentage is Omega 6 oils.

Omega 3 oils are anti-inflammatory and antioxidative. They counter the omega-6 oils.

A ketogenic diet has been used successfully for a long duration. This diet has been done to prevent seizures. A keto diet can be used to avoid or cure AD. [13]

Curcumin inhibits amyloid-beta placks and tau tangles, lowers cholesterol, prevents inflammatory activity, and mediates insulin signaling. [45]

Controlling salt intake seems unnecessary since salting to taste delivers the optimum amount for controlling AD. [19], [24]

Eliminating carbohydrate consumption to obtain at least partial ketosis and providing medium-chain triglycerides successfully stopped the progression and partially reversed cognitive decline. [32] *Age Successfully Second Edition* [4] provides a diet that meets the requirements of De la Rubia Ortí JE to prevent and reverse cognitive decline. [40] This diet in Appendix B prevents further neuron death. New brain cells are added slowly to the brain in older subjects.[25] The brain is plastic, and some recovery can be made by brain reorganization. To live a normal life without the cognitive decline of AD, the diet must be started before significant neuron death has occurred.

Added sugars that contain fructose and omega-6 seed oil consumption have increased exponentially. This increase has matched the growth of AD.

Correlation is not causation; good clinical studies and biochemical mechanisms must exist. It is not in the best interest of pharmaceutical companies to research lifestyle factors that may halt or even reverse AD progression; it is also not in the best interest of food companies to find that fructose and omega-6 oils are the cause. The lifestyle studies of the fructose and omega-6 seed oil hypothesis have used fewer subjects and have been short-duration. There is a need for long-term studies using this or a similar diet to halt the progression and reverse AD. Long-duration ketogenic diets have been used to prevent seizures and may be part of the solution to cure AD.

1. **The Mediterranean Diet (MD)**

MD is recommended in many studies, used against control in clinical studies, and is recommended in most health literature. Often it is not defined, and the reader is left to determine what it is. Is the MD lots of pasta and red wine? When the MD is defined, it is usually a diet high in fruits and vegetables with whole grain cereals, olive oil, and fish. There are many flaws in this diet description. I have been to Italy, eaten in their restaurants, visited their grocery stores, and observed what the people eat. Italian pasta and Italian bread are not whole grains. Cereals on the shelves in the United States, even when they claim to contain whole grain, typically have little whole grain and large quantities of added sugars.

Fruits and vegetables are not the same. Most vegetables have evolved to contain toxins against insects, microbes, and animals who would eat them. [8] Recommending green leafy vegetables is not specific enough. For example, spinach contains oxalic acid, and if it were a large part of a diet, oxalic acid would block iron absorption, thereby causing anemia. Fruits typically have toxins when the seeds are not developed enough to pass through the vector unharmed. Fruit seeds usually contain toxins to prevent them from being eaten. [17] Fruits are high in sugar, with fructose being the most concerning.

Some fructose from sugar will gain access to the brain, increasing appetite and blocking the signal that tells the brain to stop eating. [15] Fructose cannot be used by cells for energy. It must be converted to fat by the liver. Some of this fat is stored by the liver, causing fatty liver disease; some is released into the bloodstream as small particle triglycerides; These particles can cause arterial blockages.

We need to stop using the term Mediterranean diet and be specific when recommending a diet.

1. **A diet for AD based on the AD diet in *Age Successfully* and additional research:**

The Cunnane and the Seneff papers explain the principles of changing the brain from glucose fuel to ketone fuel to combat AD and other health problems. We need to provide medium-chain fatty acids that can be converted to ketones and reduce glucose availability to force the conversion. The conversion happens when in or partially in ketosis. This treatment is based on the theory that the brain loses its ability to use glucose and does not lose its ability to use ketones for energy. The brain can grow more cells and synapses, but this is slow. This treatment must be started before a significant part of the brain is lost. If Cunnane is right, amyloid and tau proteins can be thought of as brain scar tissue and not the cause of the problem. This diet will provide the ketones without being in full ketosis.

Stopping the loss of intellectual capacity is not easy and requires the person progressing to or with AD to put in the effort. Any attempt to cure AD will only work if the subject has a reason to be intellectually active. This need for motivation is particularly important for the spouse or caregiver. There needs to be a life purpose or life goals. If the subject is simply in a retirement facility waiting to die, they have no incentive to improve their intellectual capacity. Without a life purpose, why not have AD? In later stages, it is less stressful.

An effective AD cure requires diabetes to be cured first. The presence of significant insulin will prevent ketone metabolism.

After the diabetes is cured, start the first step to eliminate AD: take two tablespoons of Medium Chain Triglyceride (MCT) oil three times a day. [32] MCT oil can have a laxative effect and can cause digestive upset. It may need to be added incrementally.

Use coconut oil for cooking at low temperatures and virgin olive oil for higher temperatures. Eliminating omega-6 fatty acids will reduce inflammation.

Eliminate added sugars to reduce A1c.

Take 2 grams of turmeric (curcumin) daily to clear amyloid plaque proteins from the brain. [28]

Eat sufficient animal protein. For persons over 60, this can be daunting. Baum et al. recommend between 1.2 and 2 grams per day per kg for the elderly. I weigh 175 pounds (79kg) and am 83 years old. I ride my bike and work out in the gym daily. Based on that, I should consume 85 grams of protein per day. An egg has 14 grams of protein. Four oz of raw ground beef has 21 grams of protein. [2]

Take an omega-3 oil supplement that has DHA.

Maintaining an adequate fiber intake and reducing carbohydrates to less than 10% will require replacing potatoes, sweet potatoes, rice, corn, bread, carrots, beets, and other starchy foods with high-fiber vegetables. Martin-Gallausiaux et al. described the importance of short-chain triglycerides made from fiber in the colin to health [49]

Physical exercise and mental exercise are needed to keep the brain active. Both physical and mental activity encourages new brain cell formation and synapse formation.

Use intermittent fasting to clear inactive proteins and mitochondria.

Lang et al. have also proposed using diet to control AD. [46]

**Disclosures**

The author has no financial interest in anything related to this paper

References:

[1] Anderson, P. (n.d.). Gum Disease Bacteria a New Treatment Target for AD? Retrieved October 2, 2022, from https://www.medscape.com/viewarticle/963574?uac=362670CN&faf=1&sso=true&impID=3824361&src=wnl\_edit\_tpal#vp\_2

[2] Baum, J. I., Kim, I. Y., & Wolfe, R. R. (2016, June 8). Protein consumption and the elderly: What is the optimal level of intake? Nutrients. MDPI AG. https://doi.org/10.3390/nu8060359

[3] Baumgart, M., Snyder, H. M., Carrillo, M. C., Fazio, S., Kim, H., & Johns, H. (2015). Summary of the evidence on modifiable risk factors for cognitive decline and dementia: A population-based perspective. AD & Dementia, 11(6), 718–726. https://doi.org/10.1016/J.JALZ.2015.05.016

[4] *Age Successfully Second Edition*: Black, Robert Harrison: 9798646852916: Amazon.com: Pages 117-121 and 135-136 Books. (n.d.). Retrieved February 6, 2022, from <https://www.amazon.com/Successfully-Second-Robert-Harrison-Black/dp/B088T5GJ8B>

[5] Caraballo, R. (n.d.). Ketogenic Diet For Epilepsy / Seizures. Retrieved October 14, 2022, from https://my.clevelandclinic.org/health/treatments/7156-ketogenic-diet-keto-diet-for-epilepsy

[6] Chatterjee, S., Peters, S. A. E., Woodward, M., Arango, S. M., Batty, G. D., Beckett, N., … Huxley, R. R. (2016). Type 2diabetes as a risk factor for dementia in women compared with men: A pooled analysis of 2.3 million people comprising more than 100,000 cases of dementia. Diabetes Care, 39(2), 300–307. https://doi.org/10.2337/dc15-1588

[7] Cunnane, S. C., Courchesne-Loyer, A., Vandenberghe, C., St-Pierre, V., Fortier, M., Hennebelle, M., … Castellano, C. A. (2016). Can ketones help rescue brain fuel supply in later life? Implications for cognitive health during aging and the treatment of AD. Frontiers in Molecular Neuroscience, 9(JUL). https://doi.org/10.3389/fnmol.2016.00053

[8] (D, D, A, & I V, 2016) https://www.researchgate.net/publication/301646957\_A\_SYSTEMATIC\_REVIEW\_OF\_NATURAL\_TOXINS\_IN\_FOOD\_PLANTS

[9] W M A D B Fernando et al. The role of dietary coconut for the prevention and treatment of AD: potential mechanisms of action https://pubmed.ncbi.nlm.nih.gov/25997382/

[10] Juby, Angela G corresponding authors, Toni E. Blackburn, and Diana R. Mager Use of medium chain triglyceride (MCT) oil in subjects with Alzheimer’s disease: A randomized, double‐blind, placebo‐controlled, crossover study, with an open‐label extension https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8919247/

[11] Kane, M.D., R. L., Butler, Ph.D., M.B.A., M., & Fink, M.D., M.P.H., H. A. (2017). Interventions To Prevent Age-Related Cognitive Decline, Mild Cognitive Impairment, and Clinical Alzheimer’s-Type Dementia. https://doi.org/10.23970/AHRQEPCCER188

[12] Kroemer, G., López-Otín, C., Madeo, F., & de Cabo, R. (2018, October 18). Carbotoxicity—Noxious Effects of Carbohydrates. Cell. Cell Press. https://doi.org/10.1016/j.cell.2018.07.044

[13] Lambrechts, D. A. J. E., Bovens, M. J. M., De la Parra, N. M., Hendriksen, J. G. M., Aldenkamp, A. P., & Majoie, M. J. M. (2013). Ketogenic diet effects on cognition, mood, and psychosocial adjustment in children. Acta Neurologica Scandinavica, 127(2), 103–108. https://doi.org/10.1111/J.1600-0404.2012.01686.X

[14] Livingston, G., Huntley, J., Sommerlad, A., Ames, D., Ballard, C., Banerjee, S., … Mukadam, N. (2020). Dementia prevention, intervention, and care: 2020 report of the Lancet Commission. Lancet (London, England), 396(10248), 413. [https://doi.org/10.1016/S0140-6736(20)30367-6](https://doi.org/10.1016/S0140-6736%2820%2930367-6)

[15] Lowette, K., Roosen, L., Tack, J., Berghe, P. Vanden, Andrabi, S. A., Hopkins, J., … Kentish, S. (2015). NUTRITION MINI REVIEW ARTICLE Effects of high-fructose diets on central appetite signaling and cognitive function. https://doi.org/10.3389/fnut.2015.00005

[16] Ma, Qiu-Lan, et al. The Novel Omega-6 Fatty Acid Docosapentaenoic Acid Positively Modulates Brain Innate Immune Response for Resolving Neuroinflammation at Early and Late Stages of Humanized APOE-Based AD Models https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7596305/

[17] Medical News Today Apple seed toxins https://www.medicalnewstoday.com/articles/318706#risks

[18] Mehta D, Jackson R, Paul G, Shi J, Sabbagh M. Why do trials for AD drugs keep failing? A discontinued drug perspective for 2010-2015. Expert Opin Investig Drugs. 2017 Jun;26(6):735-739. doi: 10.1080/13543784.2017.1323868. PMID: 28460541; PMCID: PMC5576861.

[19] Mente, A., O’Donnell, M., & Yusuf, S. (2021, June 1). Sodium and health: Another challenge to the current dogma. European Heart Journal. Oxford University Press. https://doi.org/10.1093/eurheartj/ehaa1093

[20] Melzer, T. M., Manosso, L. M., Yau, S. Y., Gil-Mohapel, J., & Brocardo, P. S. (2021). In Pursuit of Healthy Aging: Effects of Nutrition on Brain Function. International Journal of Molecular Sciences, 22(9). https://doi.org/10.3390/IJMS22095026

[21] Mohan, D., Yap, K. H., Reidpath, D., Soh, Y. C., McGrattan, A., Stephan, B. C. M., … Pase, M. (2020). Link Between Dietary Sodium Intake, Cognitive Function, and Dementia Risk in Middle-Aged and Older Adults: A Systematic Review. Journal of AD, 76(4), 1347. https://doi.org/10.3233/JAD-191339

[22] NH Health. (2014). How much sugar do you eat? Retrieved September 8, 2019, from https://www.dhhs.nh.gov/dphs/nhp/documents/sugar.pdf

[23] NIH. (n.d.). What Happens to the Brain in AD? | National Institute on Aging. Retrieved October 2, 2022, from https://www.nia.nih.gov/health/what-happens-brain-alzheimers-disease

[24] Mente, A., O’Donnell, M., & Yusuf, S. (2021, June 1). Sodium and health: Another challenge to the current dogma. European Heart Journal. Oxford University Press. https://doi.org/10.1093/eurheartj/ehaa1093

[25] Imayoshi, I., Sakamoto, M., Ohtsuka, T., & Kageyama, R. (2009). Continuous neurogenesis in the adult brain. Development Growth and Differentiation, 51(3), 379–386. https://doi.org/10.1111/J.1440-169X.2009.01094.X

[26] O’Donnell, M., Mente, A., Rangarajan, S., McQueen, M. J., Wang, X., Liu, L., … Yusuf, S. (2014). Urinary Sodium and Potassium Excretion, Mortality, and Cardiovascular Events. New England Journal of Medicine, 371(7), 612–623. https://doi.org/10.1056/nejmoa1311889

[27] Rebello, C. J., Keller, J. N., Liu, A. G., Johnson, W. D., & Greenway, F. L. (2015, June 1). Pilot feasibility and safety study examining the effect of medium chain triglyceride supplementation in subjects with mild cognitive impairment: A randomized controlled trial. BBA Clinical. Elsevier. https://doi.org/10.1016/j.bbacli.2015.01.001

[28] Reddy, P. H., Manczak, M., Yin, X., Grady, M. C., Mitchell, A., Tonk, S., … Author, D. (2018). Protective Effects of Indian Spice Curcumin Against Amyloid Beta in Alzheimer’s Disease HHS Public Access Author manuscript. J Alzheimers Dis, 61(3), 843–866. https://doi.org/10.3233/JAD-170512

[29] Ravnskov, U., DiNicolantonio, J. J., Harcombe, Z., Kummerow, F. A., Okuyama, H., & Worm, N. (2014, April 1). The questionable benefits of exchanging saturated fat with polyunsaturated fat. Mayo Clinic Proceedings. Elsevier Ltd. https://doi.org/10.1016/j.mayocp.2013.11.006

[30] Rolland, Y., Pillard, F., Klapouszczak, A., Reynish, E., Thomas, D., Andrieu, S., … Vellas, B. (2007). Exercise program for nursing home residents with Alzheimer’s disease: a 1-year randomized, controlled trial. Journal of the American Geriatrics Society, 55(2), 158–165. https://doi.org/10.1111/J.1532-5415.2007.01035.X

[31] Roy, M., Edde, M., Fortier, M., Croteau, E., Castellano, C. A., St-Pierre, V., … Descoteaux, M. (2022). A ketogenic intervention improves dorsal attention network functional and structural connectivity in mild cognitive impairment. Neurobiology of Aging, 115, 77–87. https://doi.org/10.1016/J.NEUROBIOLAGING.2022.04.005

[32] de la Rubia Ortí JE1, García-Pardo MP2, Drehmer E1, Sancho Cantus D3, Julián Rochina M4, Aguilar MA5, H. Y. I. (n.d.). Improvement of Main Cognitive Functions in Patients with AD after Treatment with Coconut Oil Enriched Mediterranean Diet: A Pilot ... - PubMed - NCBI. Retrieved April 27, 2020, from https://www.ncbi.nlm.nih.gov/pubmed/30056419

[33] Seneff, S., Wainwright, G., & Mascitelli, L. (2011, April 1). Nutrition and AD: The detrimental role of a high carbohydrate diet. European Journal of Internal Medicine. Elsevier B.V. https://doi.org/10.1016/j.ejim.2010.12.017

[34] Tampi, R. R., Forester, B. P., & Agronin, M. (2021). Aducanumab: evidence from clinical trial data and controversies. Drugs in Context, 10. https://doi.org/10.7573/DIC.2021-7-3

[35] Taylor, M. K., Sullivan, D. K., Mahnken, J. D., Burns, J. M., & Swerdlow, R. H. (2018). Feasibility and efficacy data from a ketogenic diet intervention in Alzheimer’s disease. Alzheimer’s & Dementia: Translational Research & Clinical Interventions, 4(1), 28–36. https://doi.org/10.1016/j.trci.2017.11.002

[36] Woods, B., Aguirre, E., Spector, A. E., & Orrell, M. (2012). Cognitive stimulation to improve cognitive functioning in people with dementia. Cochrane Database of Systematic Reviews. https://doi.org/10.1002/14651858.CD005562.PUB2

[37] Xu, Q., Zhang, Y., Zhang, X., Liu, L., Zhou, B., Mo, R., … Xue, C. (2020). Medium-chain triglycerides improved cognition and lipid metabolomics in mild to moderate AD patients with APOE4−/−: A double-blind, randomized, placebo-controlled crossover trial. Clinical Nutrition, 39(7), 2092–2105. https://doi.org/10.1016/j.clnu.2019.10.017

[38] Zhan, X., Stamova, B., Jin, L. W., Decarli, C., Phinney, B., & Sharp, F. R. (2016). Gram-negative bacterial molecules are associated with AD pathology. Neurology, 87(22), 2324–2332. <https://doi.org/10.1212/WNL.0000000000003391>

[39] Sonja Sulkava, MD, PhD; Jari Haukka, PhD; Raimo Sulkava, MD, PhD; Tiina Laatikainen, MD, PhD; Tiina Paunio, MD, PhD Association Between Psychological Distress and Incident Dementia in a Population-Based Cohort in Finland [file:///C:/Users/Robert/Downloads/sulkava\_2022\_oi\_221326\_1670513501.24542.pdf](file:///C%3A/Users/Robert/Downloads/sulkava_2022_oi_221326_1670513501.24542.pdf)

[40] Black, Robert Harrison <https://www.amazon.com/Age-Successfully-Live-Long-Healthy/dp/1673645534>

[41] Poorni Sandupama1Dilusha Munasinghe1Madhura Jayasinghe Coconut oil as a therapeutic treatment for alzheimer’s disease: a review Journal of Future Foods Volume 2, Issue 1, March 2022, Pages 41-52 <https://www.sciencedirect.com/science/article/pii/S2772566922000295?dgcid=raven_sd_recommender_email>

[42] Blasbalg, T. L., Hibbeln, J. R., Ramsden, C. E., Majchrzak, S. F., & Rawlings, R. R. (2011). Changes in consumption of omega-3 and omega-6 fatty acids in the United States during the 20th century. The American Journal of Clinical Nutrition, 93(5), 950. https://doi.org/10.3945/AJCN.110.006643

[43] Chen, Y., Wang, K., Huang, T., Xie, C., & Chen, Z. (2023). Exercise interventions ameliorate neuropsychiatric symptoms in dementia: A meta-analysis. Mental Health and Physical Activity, 24, 100496. https://doi.org/10.1016/J.MHPA.2022.100496

[44]van Dyck, C. H., Swanson, C. J., Aisen, P., Bateman, R. J., Chen, C., Gee, M., … Iwatsubo, T. (2022). Lecanemab in Early Alzheimer’s Disease. The New England Journal of Medicine. <https://doi.org/10.1056/NEJMOA2212948/SUPPL_FILE/NEJMOA2212948_APPENDIX.PDF>

[45] Tang, M., & Taghibiglou, C. (2017). The Mechanisms of Action of Curcumin in Alzheimer’s Disease. <https://doi.org/10.3233/JAD-170188>

[46] Lange, K. W., Lange, K. M., Makulska-Gertruda, E., Nakamura, Y., Reissmann, A., Kanaya, S., & Hauser, J. (2017, March 1). Ketogenic diets and Alzheimer’s disease. Food Science and Human Wellness. Elsevier B.V. <https://doi.org/10.1016/j.fshw.2016.10.003>

[47] NIH. (n.d.). What Happens to the Brain in Alzheimer’s Disease? | National Institute on Aging. Retrieved February 6, 2023, from <https://www.nia.nih.gov/health/what-happens-brain-alzheimers-disease>

[48] Alves, F., Kallinowski, P., & Ayton, S. (2023). Accelerated Brain Volume Loss Caused by Anti–β-Amyloid Drugs: A Systematic Review and Meta-analysis. Neurology. https://doi.org/10.1212/WNL.0000000000207156

[49] Martin-Gallausiaux, C., Marinelli, L., Blottière, H. M., Larraufie, P., & Lapaque, N. (2021). SCFA: mechanisms and functional importance in the gut. Proceedings of the Nutrition Society, 80(1), 37–49. https://doi.org/10.1017/S0029665120006916