

(All text in blue below is quoted from this important paper by Botchway et al 2018)

Botchway, B. O. A., Moore, M. K., Akinleye, F. O., Iyer, I. C., & Fang, M. (2018). Nutrition: Review on the Possible Treatment for Alzheimer's Disease. *J Alzheimers Dis*, **61**(3), 867-883. doi:10.3233/JAD-170874

Here is the link to PubMed: <https://www.ncbi.nlm.nih.gov/pubmed/29254101>

[NOTE: The paper is not free to access online, so excerpts are given below with the author's kind permission.]

“The connection between nutrition and AD has been discussed in several published studies. In some quarters, curcumin, vitamins, and Mediterranean diet have been postulated to possibly have a preventative role in AD... this review report was centered on these three nutritional components.”



Fig. 1. Some food sources of vitamins A–E. (from Botchway et al 2018)

Dietary sources of some flavonoids:

Flavanones - Orange juice, Grapefruit juice, Lemon juice

Flavonols – Yellow onion, Curly kale, Leek, Cherry tomato, Broccoli, Tomato, Apple, Black tea infusion, Green tea infusion, Black grape, Blueberry

Flavones – Parsley, Celery, Capsicum pepper

Anthocyanidins – Aubergine, Black berry, Black currant, Blueberry, Black grape, Cherry, Rhubarb, Strawberry, Red wine, Red cabbage, Plum

Isoflavonoids - Soy cheese, Soy, Soy bean, Tofu (from Botchway et al 2018, p.872)

Role of curcumin in AD – action on glial cells and macrophages; antioxidant effect; cholesterol lowering effect; metal chelation effect; anti-inflammatory effect; action on amyloid plaques. (Botchway et al 2018, p.872)

Botchway BO, Iyer IC (2017) Alzheimer's disease – the past, the present and the future. *Sci J Clin Med* 6, 1-19.

Vitamins

"The use of vitamin supplementation as an adjuvant intervention has been examined, some of which have been postulated to be effective" Bhatti AB, Usman M, Ali F, Satti SA (2016) Vitamin supplementation as an adjuvant treatment for Alzheimer's disease. *J Clin Diagn Res* 10, OE07-OE11.

"Lopes et al.'s systematic review suggested that vitamins, among other nutrients, play an extensive role in the development of AD treatment and management as an examined AD population had significantly lower plasma levels of folate as well as vitamins B12, C, and E in comparison to a controlled population. The study also concluded lower levels were indications of patients with AD, possibly having impaired systemic availability of several nutrients." Lopes de Silva S, Vellas B, Elemans S, Luchsinger J, Kamphuis P, Yaffe K, Sijben J, Groenendijk M, Stijnen T (2014) Plasma nutrient status of patients with Alzheimer's disease: Systematic review and meta-analysis. *Alzheimers Dement* 10, 485-502.

"Antioxidants are molecules that inhibit oxidation of other molecules. They are widely employed and investigated for preventative benefits to diseases including AD, along with other neurodegenerative conditions. Antioxidants protect against extracellular and intracellular reactive oxygen species (ROS) and H₂O₂-cell-damaging radicals, which are by products generated from normal cell metabolism." Pagani L, Eckert A (2011) Amyloid-beta interaction with mitochondria. *Int J Alzheimers Dis* 2011, 925050.

Low levels of vitamin A are a risk factor for AD and a major problem in the aging population.... The most useable form of vitamin A is retinol, which is converted by the body into retinal and retinoic acid (RA). Botchway (2018)

"RA is a subset of carotenoids and retinoids. A derivative of RA has been found to cause reduction in both IL-6 and IL-1 levels with several studies looking into its role as a therapeutic option for AD". Shudo K, Nakagomi M, Yamagata N, Fukasawa H (2009) Towards retinoid therapy for Alzheimer's disease. *Curr Alzheimer Res* 6, 302-311.

Kagechika H, Kawachi E, Fukasawa H, Saito G, Iwanami N, Umemiya H, Hashimoto Y, Shudo K (1997) Inhibition of IL-1-induced IL-6 production by synthetic retinoids. *Biochem Biophys Res Commun* 231, 243-248.

Omega-3s

"Researchers have linked high intake of omega-3s to a possible reduction in risk of dementia or cognitive decline" Jicha GA, Markesbery WR (2010) Omega-3 fatty acids: Potential role in the management of early Alzheimer's disease. *Clin Interv Aging* 5, 45-61. [and] Quinn JF, Raman R, Thomas RG, Yurko-Mauro K, Nelson EB, Van Dyck C, Galvin JE, Emond J, Jack CR Jr, Weiner M, Shinto L, Aisen PS (2010) Docosahexaenoic acid supplementation and cognitive decline in Alzheimer disease: A randomized trial. *JAMA* 304, 1903-1911.

Ginkgo biloba

"Several epidemiological and clinical studies have revealed the baulking features of turmeric in AD as well as the potentiality of ameliorating AD." McBarron J (2012) Curcumin: The 21st Century Cure (2nd ed., p. 2). Kathleen Barnes, Brevard, NC.

DeKosky ST, Williamson JD, Fitzpatrick AL, Kronmal RA, Ives DG, Saxton JA, Lopez OL, Burke G, Carlson MC, Fried LP, Kuller LH, Robbins JA, Tracy RP, Woolard NF, Dunn L, Snitz BE, Nahin RL, Furberg CD; Ginkgo Evaluation of Memory (GEM) Study Investigators (2008) Ginkgo biloba for prevention of dementia: A randomized controlled trial. *JAMA* 300, 2253-2262.

Snitz BE, O'Meara ES, Carlson MC, Arnold AM, Ives DG, Rapp SR, Saxton J, Lopez OL, Dunn LO, Sink KM, DeKosky ST; Ginkgo Evaluation of Memory (GEM) Study Investigators (2009) Ginkgo biloba for preventing cognitive decline in older adults: A randomized trial. *JAMA* 302, 2663-2670

Oken BS, Storzbach DM, Kaye JA (1998) The efficacy of Ginkgo biloba on cognitive function in Alzheimer disease. *Arch Neurol* 55, 1409-1415.

The Preventive Mechanisms of AD (this excerpt is from Botchway, B. O. A., & Iyer, I. C. (2017). Alzheimer's Disease – The Past, the Present and the Future. *Science Journal of Clinical Medicine*, 6(1). doi:10.11648/j.sjcm.20170601.11

"...there are also some suggested preventive mechanisms that reduce the likelihood of developing AD.... it is unclear at the moment which of the preventive mechanisms is more effective or better than the other. Nevertheless, some of the preventive mechanisms suggested are centered on lifestyle changes and diet."

(Leonard, 2016) “The lifestyle changes include mental and physical exercises. Mental exercises such as general reading, playing board games as well as playing instruments helps in keeping the brain active, thereby reducing the risk of getting AD. Besides enhancing the blood flow, physical exercise also aids in the oxygen flow within the brain tissues, which in turn decreases the risk of developing the disease (Leonard, 2016).”

“In the dietary department, the Mediterranean diet, of which constitutes a small amount of red meat coupled with conglomerations of fruits, vegetables, whole grains, fish and shellfish as well as healthy fats, has been suggested to have a hand in delaying the cognitive atrophy symptom associated with AD (Solfrizzi 2011). Other research studies have also postulated that by lowering the homocysteine levels, an amino acid that is obtained predominantly from the consumption of meat, in the blood, the risk of getting AD will reduce.” (McCaddon 2006) Leonard, W. *Alzheimer’s disease prevention*. Retrieved May 1, 2016, from Healthline, <http://www.healthline.com/health/alzheimers-disease-prevention>.

Solfrizzi, V., Panza, F., Frisardi, V., Seripa, D., Logroscino, G., Imbimbo, B. P., & Pilotto, A. (2011). Diet and Alzheimer’s disease risk factors or prevention: The current evidence. *Expert Review of Neurotherapeutics*, 11(5), 677–708. Doi:10.1586/ern.11.56.

McCaddon, A. (2006). Homocysteine and cognitive impairment; a case series in a General Practice setting. *Nutrition Journal*, 5(6), DOI:10.1186/1475-2891-5-6.

Huperzine A

“Huperzine A, another Chinese herb, is a moss extract that has been used in traditional Chinese medicine for centuries. Its pharmacological properties include being an acetylcholinesterase inhibitor, which happens to be one class of FDA-approved AD medications...” Li J, Wu HM, Zhou RL, Liu GJ, Dong BR (2008) Huperzine A for Alzheimer’s disease. *Cochrane Database Syst Rev* 2, CD005592.

Souvenaid

“Souvenaid is a 125-ml (125-kcal) once-daily drink that has now become available and used as medical food ... combines a variety of substrates, including uridine monophosphate, phospholipid, choline, and omega-3 fatty acids, vitamins, and antioxidants, which are thought to be essential for formation of synaptic membranes [Thaipisuttikul and Galvin 2012]. The AD brain has shown evidence of synaptic failure, and this is one of the earliest manifestations of the disease [Serrano-Pozo 2011]. The constituent of Souvenaid is expected to generate new synaptic connections such as dendritic spine growth. Souvenaid is currently being highly recommended as one of the leading supplements in AD treatment.” Thaipisuttikul P, Galvin JE (2012) Use of medical foods and nutritional approaches in the treatment of Alzheimer’s disease. *Clin Pract* (London) 9, 199-209.

Serrano-Pozo A, Frosch MP, Masliah E, Hyman BT (2011) Neuropathological alterations in Alzheimer disease. *Cold Spring Harbor Perspectives in Medicine* 1, A006189.

Vitamins C and E

“Dietary supplements and vitamins containing folic acid and vitamin C have been shown to have remarkable effects in the prevention of AD and improve memory loss, on the basis that folic acid reduces homocysteine levels, and vitamin C, when combined with vitamin E, reduces the risk of AD.”

MEDITERRANEAN DIET

“The Mediterranean diet (MeDi) is adapted from eating patterns seen in Italy, Spain, Greece, and other Mediterranean countries. The diet involves high intake of legumes, olive oil, fruits, nuts, vegetables, and cereals, moderate consumption of fish and wine, as well as low intake of dairy products, red meat, processed meats, and sugars. Research has also indicated that greater adherence to MeDi is associated with reduced risk of developing forms of dementia such as AD.” Scarmeas N, Stern Y, Tang MX, Mayeux R, Luchsinger JA (2006) Mediterranean diet and risk for Alzheimer’s disease. *Ann Neurol* 59, 912-921.

“the diet is rich in mono-unsaturated fatty acids and fish, low in levels of saturated fat, high in levels of antioxidants such as vitamin C, vitamin E, complex phenols, carotenoids, and flavonoids, as well as high levels of vitamin B12 and folate” Liyanage T, Ninomiya T, Wang A, Neal B, Jun M, Wong MG, Jardine M, Hillis GS, Perkovic V (2016) Effects of the Mediterranean diet on cardiovascular outcomes-a systematic review and meta-analysis. *PLoS One* 11, e0159252.



An illustration of a typical Mediterranean diet. Printed in Botchway 2018, illustration is from:

Willett WC, Sacks F, Trichopoulos A, Drescher G, Ferro-Luzzi A, Helsing E, Trichopoulos D (1995) Mediterranean diet pyramid: A cultural model for healthy eating. *Am J Clin Nutr* 61, 1402S-1406S.

“...the micronutrients vitamins A, C, and E, are richly provided through the MeDi. These vitamins have been shown to have antioxidative properties. Similarly, carotenoids and flavonoids are dietary antioxidants. Several studies have illustrated antioxidants such as vitamins intake could be associated with reduced incidence of dementia [Morris 2005], and specifically reduced incidence of AD [Devore 2010].” “...research findings have also suggested that vitamin intake from food sources are more effective than those received via supplementation... [Devore] showed that vitamin E and other antioxidants taken through supplementation do not show improvement in AD symptoms” Morris MC, Evans DA, Tangney CC, Bienias JL, Wilson RS, Aggarwal NT, Scherr PA (2005) Relation of the tocopherol forms to incident Alzheimer disease and to cognitive change. *Am J Clin Nutr* 81, 508-514.

Devore EE, Grodstein F, van Rooij FJ, Hofman A, Stampfer MF, Witteman JC, Breteler MM (2010) Dietary antioxidants and long-term risk of dementia. *Arch Neurol* 67, 819-825.

“Vitamin E from food sources, such as that obtained from MeDi diet (nuts, vegetables, fruits) are in the form of tocopherols and tocotrienols. As such, full range of vitamin E is consumed” “ In contrast, vitamin E intake from supplements provides only alpha-tocopherols.” Huang HY, Appel LJ (2003) Supplementation of diets with alpha-tocopherol reduces serum concentrations of gamma- and delta-tocopherol in humans. *J Nutr* 133, 3137-3140.

“The reduced range of vitamin E found in supplementation might explain the reduced health benefits accompanying supplements in comparison to natural vitamin E intake. Complex phenols and olive oil as well as carotenoids are also antioxidants consumed in MeDi. Olive oil has been found to increase enzymes involved in antioxidation, such as paraoxonase.” Blum S, Aviram M, Ben-Amotz A, Levy Y (2006) Effect of a Mediterranean meal on postprandial carotenoids, paraoxonase activity and C-reactive protein levels. *Ann Nutr Metab* 50, 20-24.

“MeDi is also characterized by its lowfat intake, in which low proportions of consumed fats are saturated fats, with higher proportions being mono-unsaturated fats. Olive oil is the major source of fats in MeDi. Additionally, fish is another source of fat that provides low amounts of saturated fat in comparison with poultry. The association between dietary fat intake and AD development has been studied. Morris et al. 2003 found a 60% reduction in risk of developing AD when n-3 polyunsaturated fatty acids and fish were consumed at least once a week, in comparison to when they were rarely or never consumed.” Morris MC, Evans DA, Bienias JL, Tangney CC, Bennett DA, Aggarwal N, Schneider J, Wilson RS (2003) Dietary fats and the risk of incident Alzheimer disease. *Arch Neurol* 60, 194-200.

“...individuals consuming increased saturated fats and trans-unsaturated fats showed increased risk of AD. However, those consuming high intake of omega-6-polyunsaturated and monounsaturated fats had a significantly lowered risk of AD” [Morris 2003]

“some research studies have found no association between the MeDi and risk of developing dementia”

Pauwels EK (2011) The protective effect of the Mediterranean diet: Focus on cancer and cardiovascular risk. *Med Princ Pract* 20, 103-111.

“Consumption of vegetable fats as well as high ratio of poly-unsaturated to saturated fats has also been associated to reduced AD risk [Morris 2003]. Studies have found a possible mechanism by which poly and mono-unsaturated fats reduce AD risk. Unsaturated fatty acids may be protective due to its role in maintaining the integrity of neuronal membrane structures and in the regulation of synaptic membranes and neuronal transmission [Panza 2004; Solfrizzi 2003]. Panza F, Solfrizzi V, Colacicco AM, D’Introno A, Capurso C, Torres F, Del Parigi A, Capurso S, Capurso A (2004) Mediterranean diet and cognitive decline. *Public Health Nutr* 7, 959-963.

Solfrizzi V, Panza F, Capurso A (2003) The role of diet in cognitive decline. *J Neural Transm (Vienna)* 110, 95-110.

“Inflammation and inflammatory mediators, also involved in the pathogenesis of AD, are associated with cognitive decline” Akiyama H, Barger S, Barnum S, Bradt B, Bauer J, Cole GM, Cooper NR, Eikelenboom P, Emmerling M, Fiebich BL, Finch CE, Frautschy S, Griffin WS, Hampel H, Hull M, Landreth G, Lue L, Mark R, Mackenzie IR, McGeer PL, O’Banion MK, Pachter J, Pasinetti G, Plata-Salman C, Rogers J, Rydel R, Shen Y, Streit W, Strohmeyer R, Tooyoma I, Van Muiswinkel FL, Veerhuis R, Walker D, Webster S, Wegrzyniak B, Wenk G, Wyss-Coray T (2000) Inflammation and Alzheimer’s disease. *Neurobiol Aging* 21, 383-421.

Yaffe K, Kanaya A, Lindquist K, Simonsick EM, Harris T, Shorr RI, Tylavsky FA, Newman AB (2004) The metabolic syndrome, inflammation, and risk of cognitive decline. *JAMA* 292, 2237-2242.

“IL-6 cytokine is another inflammatory mediator that has been associated with increased decline in cognitive functioning [Weaver 2002] together with increased risk of dementia [Engelhart 2004]. Adherence to MeDi diet has been found to significantly reduce levels of IL-6 [Esposito 2004] as well as curtail other inflammatory markers, such as white blood cell count.” [Chrysohoou 2004] Weaver JD, Huang MH, Albert M, Harris T, Rowe JW, Seeman TE (2002) Interleukin-6 and risk of cognitive decline: MacArthur studies of successful aging. *Neurology* 59, 371-378.

Engelhart MJ, Geerlings MI, Meijer J, Kiliaan A, Ruitenberg A, Van Swieten JC, Stijnen T, Hofman A, Wittteman JC, Breteler MM (2004) Inflammatory proteins in plasma and the risk of dementia: The Rotterdam Study. *Arch Neurol* 61, 668-672.

Esposito K, Marfella R, Ciotola M, Di Palo C, Giugliano F, Giugliano G, D’Armiento M, D’Andrea F, Giugliano D (2004) Effect of a Mediterranean-style diet on endothelial dysfunction and markers of vascular inflammation in the metabolic syndrome: A randomized trial. *JAMA* 292, 1440-1446.

Chrysohoou C, Panagiotakos DB, Pitsavos C, Das UN, Stefanadis C (2004) Adherence to the Mediterranean diet attenuates inflammation and coagulation process in healthy adults: The ATTICA Study. *J Am Coll Cardiol* 44, 152-158.

“Components of MeDi, such as extra virgin olive oil, wine, and carotenoids supplemented through the diet, have been found to be associated with reduced IL-6 and thus, minimized inflammation.”

Bertelli AA, Migliori M, Panichi V, Longoni B, Origlia N, Ferretti A, Cuttano GM, Giovannini L (2002) Oxidative stress and inflammatory reaction modulation by white wine. *Ann NY Acad Sci* 957, 295-301.

“In addition to extra virgin olive oil providing anti-inflammatory components, Oleocanthal, a phenylethanoid, has been postulated to have the potentiality of abating the risk of AD. The results of Abuznait et al....” Abuznait AH, Qosa H, Busnena BA, El Sayed KA, Kaddoumi A (2013) Olive-oil-derived oleocanthal enhances -amyloid clearance as a potential neuroprotective mechanism against Alzheimer’s disease: In vitro and in vivo studies. *ACS Chem Neurosci* 4, 973-982.

“...illustrated that Oleocanthal is in fact active in the clearance of (Amyloid beta) plaques and tau proteins, both of which are characteristic features in AD neuropathology”. Hardy J, Selkoe DJ (2002) The amyloid hypothesis of Alzheimer’s disease: Progress and problems on the road to therapeutics. *Science* 297, 353-356.