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Are certain life style habits associated with lower Alzheimer disease risk?

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Abstract

As the number of patients with Alzheimer disease is expected to grow, finding ways to prevent and lower the risk of Alzheimer disease becomes a crucial matter. Risk factors for developing AD have been identified including health conditions, dietary habits, genetics and heredity, gender, education, age, and lifestyle. Interventions targeted at some of these risk factors may offer opportunities for development of an optimal preventive strategy. Life style habits which include dietary habits and physical activities appear to have positive effect on modifying many risk factors. Studies have shown controversial results when it comes to the relation between the adherence to a Mediterranean diet and /or physical activity and the incidence of Alzheimer disease. Many population-based studies reported the positive association between antioxidants intake (like Vitamin E and C), and polyunsaturated fatty acids whether it is from the diet or supplements on the cognitive performance. Future investigations should aim to determine objectively whether lifestyle modification through diet, exercise, or vitamins/supplements truly exert risk reduction or outright prevention. In this review, life-style habits are reviewed as they pertain to influence on risk of developing AD as well as on cognitive decline. Epidemiological studies and animal studies are reviewed.

Keywords

Alzheimer's; prevention; lifestyle; risk; Mediterranean diet; physical activity

Introduction

Due to the aging of the population and other factors, the incidence and prevalence of Alzheimer disease (AD) is expected to increase. Identification and modification of risk factors might prove beneficial in preventing AD, since the current treatments have modest effects on symptoms and do not significantly alter the outcome. Aggressive management of vascular risk factors including hypertension, diabetes, dyslipidemia and obesity, or engaging in life style habits-including diet and physical activity present therapeutic targets in the development of a prevention strategy [1]. Recent findings showed that elderly persons from different ethnicities (for example African Americans and Japanese living in the USA [2, 3, 4] have higher prevalence of AD than those still living in their countries of origin, suggesting that diet and lifestyle exert more influence than genetics [5].

In this article we review the most recent studies in how lifestyle habits – adherence to a Mediterranean diet, antioxidant supplements intake and higher physical activity - might have an effect on lowering the risk of AD either combined or each one independently.

The influence of diet on AD risk

The Mediterranean diet

Our dietary intake might exert a significant influence on the risk of developing or conversely preventing cognitive decline and Alzheimer disease [6, 7]. Dietary patterns normally reflect the individual knowledge relating to a favorable or unpleasant health effect of a variety of dietary constituents. One of these dietary patterns is the Mediterranean diet, which has been getting a great attention recently.

The traditional Mediterranean diet consists of high consumption of plant food (Vegetables, fruits, legumes and cereals), high intake of olive oil as the major source of monounsaturated fatty acids (MUFA) but low intake of saturated fat, moderate intake of fish as a source of n-3 poly unsaturated fatty acids (PUFA), low to moderate intake of dairy products (mostly in the form of cheese or yogurt), low consumption of meat and poultry and low consumption of wine, generally during meals [8].

The main question is: does adherence to a Mediterranean diet protect against cognitive impairment and lower the risk of Alzheimer disease and all cause of dementia? In a population-based cross-sectional cohort study conducted in Greece, adherence to a Mediterranean type diet has been associated with reduced risk of cardiovascular, neurodegenerative disease, and overall longer survival [8, 9]. Two recent studies were conducted to uncover the real value of the Mediterranean diet on reducing the risk of Alzheimer disease in different countries. The first prospective cross-sectional cohort study was done on multiethnic 2258 non-demented elderly individuals from New York. Subjects were followed for an average 4 years (range 0.2 –13.9). The clinical, demographic and dietary characteristics revealed that subjects who developed AD were older, less educated, had a lower body mass index, and had lower Mediterranean diet score [10]. This indicates that subjects with AD were less likely to adhere to the Mediterranean diet. The clearest association was found between the higher adherence to a Mediterranean diet and decrease risk of Alzheimer disease in this study. Compared with subjects in the lowest MeDi tertile, subjects in the middle MeDi tertile had a hazard ratio of 0.85 (95% confidence interval, 0.63–1.16) and those at the highest tertile had a hazard ratio of 0.60 (95% confidence interval, 0.42–0.87) for AD (p for trend=0.007) [10]. This was corroborated by another study by the same group [11]. The risk reduction exceeded 50%. The protective effects of adherence to the Mediterranean diet also reduced the risk of development of Mild Cognitive Impairment (MCI) suggesting that intervening early might even diminish risk of developing prodromal AD [12].

The second prospective longitudinal cohort study examined 1410 nondemented elderly individuals from Bordeaux, France, who were reexamined at least once over 5 years. Four neuropsychological tests were used to evaluate the cognitive ability including The Mini Mental State Examination (evaluates global cognitive performance), Isaacs Set Test (evaluates verbal fluency), Benton Visual Retention Test (evaluates immediate visual memory), and Free and cued Selective Reminding Test (evaluates verbal episodic memory). 66 individuals developed AD during the 5 years follow up, and they were older than those remained free from dementia. The major finding of this study was that higher adherence to the Mediterranean diet was associated with fewer errors and slower decline on MMSE but exerted no positive protective benefits on the other cognitive tests [13]. The same group of investigators assessed a total of 8,085 nondemented participants aged 65 and over were

included in the Three-City cohort study in Bordeaux, Dijon, and Montpellier (France) in 1999–2000 and had at least one re-examination over 4 years (rate of follow-up 89.1%): Daily consumption of fruits and vegetables was associated with a decreased risk of all cause dementia (hazard ratio [HR] 0.72, 95% CI 0.53 to 0.97) in fully adjusted models. Weekly consumption of fish was associated with a reduced risk of AD (HR 0.65, 95% CI 0.43 to 0.994) and all cause dementia but only among ApoE ϵ 4 noncarriers (HR 0.60, 95% CI 0.40 to 0.90). Regular use of omega-3 rich oils was associated with a decreased risk of borderline significance for all cause dementia (HR 0.46, 95% CI 0.19 to 1.11). The investigators concluded that frequent consumption of fruits and vegetables, fish, and omega-3 rich oils may decrease the risk of dementia and Alzheimer disease, especially among ApoE ϵ 4 noncarriers [Barberger-gateau et al 2007].(14)

Though the findings are somewhat disparate, several explanations could arise to explain the difference between the US and French study: first, the length of the follow up which was up to 13–16 years in the US study vs. 5–6 years in the French study. Additionally, the dietary pattern that has specific characteristics in each country may lead to misclassification of the data, and miss obvious associations [13,15].

Diets high in saturated fat

Now researchers have reason to believe that the presence of saturated fats in our diets might also affect memory function, and possibly increase people's risk of developing Alzheimer's disease [16–18]. Much, but not all, of the evidence comes from animal studies. In these studies, mice and rats were fed diets of different fat levels and then given learning and memory tests; the ones fed a high proportion of saturated fat displayed worse learning and memory than those on the lower-fat diets.

In one study performed on rats, investigators examined whether the adverse effects were from saturated fat specifically, or from any fat at all. One group of rats was fed coconut oil, known for its high saturated fat content, for eight weeks. Another group was fed soybean oil, low in saturated fat and high in unsaturated fat, for the same amount of time. After eight weeks, the animals fed the coconut oil had higher triglycerides, higher total cholesterol, and higher low-density lipoproteins. The rats fed the diet high in soybean oil did much better on memory and learning tests than did the rats fed the diet high in saturated fat [19]. In another study, Tg mice fed a diet high in saturated fat and cholesterol, with a control group of mice who did not receive the fatty diet. After two months, the mice were tested for memory-related tasks. Those that had been fed the diet of saturated fat were not able to remember the tasks, but the control group could perform them [20]. In another study, when brains of rats were examined, researchers found increased levels of the toxic beta-amyloid protein in the mice fed the high-saturated-fat diet and this might be altered by a ketogenic diet [21]. These data suggest a link between diets high in saturated fat and the development of Alzheimer's changes in the brain.

Researchers found that people who were ApoE ϵ 4 carriers and who had also high intakes of saturated fat had an increased risk for the development of Alzheimer's disease, compared with ApoE ϵ 4 carriers who had a lower intake of saturated fat. The intake of unsaturated fats, on the other hand, did not appear to influence the odds of developing Alzheimer's disease among ϵ 4 carriers and noncarriers [22]. But researchers in the Rotterdam population study found no cross-sectional association between high levels of saturated fat intake and an increased risk of dementia, complicating what seemed to be a clear link in the rat and mice studies [23].

Dietary Omega 3 Fatty Acids (FAs)

The Mediterranean diet is rich in fatty acids, which are essential components for the nervous system. They play an important role in brain development, and possess neuroprotective properties [24, 25]. Small amounts from fatty acids in the diet enable organelle normal growth. Important long-chain omega-3 fatty acids include docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA), which are synthesized from α -linolenic acid while, Omega-6 fatty acids include linoleic acid, γ -linolenic acid and arachidonic acid. The rate of the inner conversion of DHA and EPA appears to be not enough which makes dietary intake is the main source [26].

Several studies mention the benefits of fish consumption as a main source of omega 3-fatty acids. They have several mechanism of action on the brain and vascular system (Figure) with a tendency to reduce cerebrovascular and cardiovascular risk factors [27 28]. Research suggests that the effect of omega 3 fatty acids might limit Alzheimer disease pathology by reducing amyloid formation, minimizing aggregation into plaques, and increasing its clearance [29 30]

Animal studies have shown that dietary enhancement of DHA (a long-chain omega 3 (PUFA)) improves cognitive performance and slows Alzheimer's pathology, these findings might share similar preventative benefits in humans [31]. Besides, with aging, and especially in Alzheimer patients, DHA levels in the brain tend to decrease, which suggests that this drop might contribute to the cognitive impairment [32 33]. Observational studies showed that serum cholesteryl ester-EPA and DHA levels were significantly lower in all MMSE score quartiles of patients with Alzheimer's disease compared with control values [33]. In a study from Chicago, total intake of Omega 3 polyunsaturated fatty acids was associated with reduced risk of Alzheimer disease, as was intake of DHA. EPA was not associated with Alzheimer disease. The associations remained unchanged with additional adjustment for intakes of other dietary fats and of vitamin E and for cardiovascular conditions [17]. In a longitudinal study in Italy, high MUFA and PUFA energy intakes and total energy intake were significantly associated with a better cognitive performance in a 8.5-year follow-up. In this prospective population-based study on older nondemented subjects with a typical Mediterranean diet, high MUFA and PUFA intakes appeared to be protective against age related cognitive decline (34)[Solfrizzi et al 2006]. Unfortunately, clinical trials have failed to establish a significant benefit for the use of DHA, EPA or other forms of omega-3 fatty acids for the treatment of Alzheimer disease (35)[Van De Rest et al 2008].

Alcohol Consumption

Moderate intake of alcohol especially with meals is a significant characteristic of the Mediterranean diet. It may have a protective effect on the cognitive performance as it has on cardiovascular disease [36]. Several studies suggest that moderate drinkers do better on cognitive tests than nondrinkers [37] and this might be attributed to some extent to alcohol-induced elevations in high density lipoprotein (HDL) cholesterol and reductions in fibrinogen and other thrombotic factors [36]. In the Nurses Health Study, which longitudinally followed the dietary, health, and cognitive patterns of twelve thousand nurses between the ages of seventy and eighty-one for more than two decades, participants who reported drinking up to 15 grams of alcohol per day (about one alcoholic beverage – see sidebar) showed markedly better cognitive scores than those who reported not drinking at all. Women who consumed one drink per day had a 20 percent lower risk of cognitive decline than did those who did not drink alcohol regularly [37]. Researchers determined that the type of alcohol consumed did not influence the effect on cognitive scores, nor did the presence of the ApoE ϵ 4 genotype. In another cross-sectional study from New York City, up to three servings of alcohol daily reduced the risk of developing AD in non ApoE ϵ 4

carriers [38]. Therefore, moderate intake of alcohol (consume less than 15.0 g of alcohol per day) may also help preserve brain vasculature, may prevent subclinical strokes, and could result in better cognitive function [37].

Supplements

Several studies suggest that free radicals play an important role in the pathogenesis of the neurodegenerative disorders including Alzheimer disease. Damage and oxidation of mitochondria and nuclear DNA was found in many Alzheimer disease patients [39]. In addition to that, the use of antioxidants and free radicals scavengers has been shown to reduce β -amyloid toxicity in AD patients which has raised the therapeutic expectations of their use [39, 40]. The free radical scavenging supplements that have theoretical benefit in clinical studies of Alzheimer disease include: Vitamin E (α -tocopherol), Selegiline (monoamine oxidase inhibitor), and *Ginkgo biloba* extract EGb 761.

Ginkgo Biloba

Ginkgo biloba is one of the most popular and widely studied brain supplements in the world. The extract from ginkgo tree leaves, first used in ancient Chinese medicine, is known primarily for its brain benefits, and is commonly prescribed overseas for circulatory health, since it increases blood flow. Ginkgo has also been shown to have, in varying degrees, beneficial effects on memory, concentration, and other cognitive conditions, and has been used for treating various health conditions such as vertigo, altitude sickness, tinnitus (ringing in the ears), and premenstrual syndrome (a.k.a. PMS). Ginkgo biloba contains flavonoids which act as free-radical fighting scavengers [41].

In a longitudinal study in Pacquid, France, dietary intake of flavonoids was associated with a 50 percent cut in the risk of developing dementia over the course of five years [42 43]. Another study showed that dietary consumption of flavonoids was associated with a 46 percent risk reduction for developing Alzheimer's.

In 1997, the *Journal of the American Medical Association* reported some stabilization of cognitive decline in Alzheimer's and vascular dementia patients [44]. But in a 2002 study in the same journal, ginkgo showed no appreciable cognitive effect among nondemented subjects [45]. Another trial showed a positive outcome on cognitive decline which is comparable to the results obtained with tetrahydroaminoacridine [46].

However, the latest data suggests that ginkgo biloba is not protective against development of AD or cognitive decline. A randomized, double-blind, placebo-controlled clinical trial was conducted with 3069 subjects aged 75 years or older with normal cognition ($n = 2587$) or MCI ($n = 482$) at study entry and assessed every 6 months for incident dementia. They were randomized to a twice-daily dose of 120-mg extract of *G. biloba* ($n = 1545$) or placebo ($n = 1524$). The overall dementia rate was 3.3 per 100 person-years in participants assigned to *G. biloba* and 2.9 per 100 person-years in the placebo group. The hazard ratio (HR) for *G. biloba* compared with placebo for all-cause dementia was 1.12 (95% confidence interval [CI], 0.94–1.33; $P = .21$) and for AD, 1.16 (95% CI, 0.97–1.39; $P = .11$). *G. biloba* also had no effect on the rate of progression to dementia in participants with MCI (HR, 1.13; 95% CI, 0.85–1.50; $P = .39$). The investigators concluded that *G. biloba* at 120 mg twice a day was not effective in reducing either the overall incidence rate of dementia or AD incidence in elderly individuals with normal cognition or those with MCI [47].

Vitamin E and Vitamin C

Vitamin E is a vital component in individual's diet. Its importance is related to its fat-soluble property. It enters the brain and exerts its antioxidant activity in cell membranes easily.

Nutritional requirements of Vitamin E vary. The recommendations in the USA for daily allowances are 15 IU (10 mg of alpha-tocopherol) for men and 12 IU (8 mg alpha-tocopherol) for women, increasing to 15 IU during pregnancy and 18 IU during lactation. High doses might be toxic and may cause gastrointestinal symptoms. Therefore, the use of Vitamin E should be controlled in order to be well tolerated [48] and in order to reduce the risk of cardio-toxicity [49].

In the Cache County Study, a large cohort was investigated cross-sectionally for the association between the use of Vitamin E, Vitamin C and the prevalence and incidence of Alzheimer disease [50]. Both prevalence and incidence data suggested that the use of vitamin E and C supplements in combination was linked to reduced incidence of AD. However, the results were not significant for reducing the risk of AD when with the use of each vitamin was assessed individually. It may also suggest that the protective effects of vitamins E and C against the disease will be more robust when taken together in higher doses [50]. Furthermore, the study showed no association between B – complex supplement intake and Alzheimer disease risk [50].

In other randomized controlled trials results have been inconsistent with Cache county study, which suggest no relationship between vitamin E, and C supplementation and cognitive performance [51]. As Vitamin C (ascorbic acid) is water soluble component that is excreted rapidly after intake, suggestions that its effect as antioxidant might be limited to the reduction of the lipid-soluble vitamin E after it has been oxidized [52].

Vitamin E and Selegiline were tested in a double blind study done on 342 moderately severe Alzheimer patients, results showed a delay in the occurrence of the following outcomes in the vitamin E group at 2000 IU daily: death, institutionalization, loss of the ability to perform basic activities of daily living, and severe dementia. These data provided the impetus supporting the role of antioxidants in slowing the progress of the disease. However, they didn't show any significant effect on cognitive tests [53]. However, in the MCI trial assessing the effect of vitamin E, donepezil and placebo on 760 subjects with MCI, vitamin E had no objective evidence of benefit [54].

Therefore, it remains unclear whether the observed associations between antioxidant use and cognitive decline are causal or are due to uncontrolled confounding factors and/or different kind of biases [52].

Folic Acid

Folic acid, sometimes called folate, is a water-soluble vitamin that is often dispensed with vitamin B₁₂ (cyanocobalamin) and other B vitamins. Folic acid deficiency is rare in the United States today, a fact that is attributed to the nationwide supplementation of this vitamin in grain products. Since 1998, U.S. commercially produced cereals and breads have been fortified with folic acid, a relatively simple and low-cost preventive action that has significantly reduced the prevalence of folate deficiency and hyperhomocysteinemia in the United States.

In the literature, folic acid is one of the few vitamins whose specific isolated total intake has been significantly associated with a lowered risk of Alzheimer's. Low folate status is associated with poor cognitive function and dementia in the elderly, whereas the literature suggests that supplement-delivered folic acid may confer some protective effect for Alzheimer's risk. In the Baltimore Longitudinal Study of Aging, participants who took folic acid at or above the RDA (400 mcg daily) had a 55 percent reduced risk of developing Alzheimer's [55]. Another study from New York confirmed the protective effects of folic acid consumption. In that cross-sectional study, the group with the highest folic acid intake

had a 50 percent risk reduction, compared with the group taking the lowest amount of folic acid. In the study, the highest amount of folic acid was defined as greater than 480 mcgs daily [56].

Although it is easy to feel optimistic about taking B vitamins and folic acid, not all studies identify a benefit. Recently, the results of a two-year clinical trial published in the *New England Journal of Medicine* found that lowering homocysteine levels in elderly patients with B₆, B₁₂, and folate resulted in no appreciable cognitive improvement. For two years, the investigators studied nearly three hundred participants over sixty-five years old with high homocysteine; half were treated with the vitamin supplements and half given a placebo. The researchers found no difference between the two groups' cognitive tests given at the one- and two-year marks [55]. In a large double blind placebo controlled randomized clinical trial investigating the effects of folic acid in AD, doses approaching 5000mcg had no clinical benefit [57].

Curcumin and Resveratrol

There is also growing interest in curcumin and resveratrol. The interest of curcumin comes from epidemiological evidence that the incidence of AD is lower in India. Curcumin exerts anti-inflammatory, anti-oxidant, and anti-amyloid properties [58]. Clinical trials are underway examining the effects of curcumin as a treatment for AD. Prevention trials have been proposed.

Resveratrol is a naturally occurring *phytoalexin* produced by some higher plants. Phytoalexins are chemical substances produced by plants as a defense against infection by microorganisms, such as fungi. Scientific studies have reported a number of beneficial health effects. Resveratrol has been shown to have anticancer, antiviral, neuroprotective, antiaging, anti-inflammatory and life-prolonging effects [59 64]. Epidemiological, in vitro, and animal studies suggest that a high resveratrol intake may contribute to a reduced incidence of cardiovascular disease, and a reduced risk for cancer. Newer evidence suggest anti-Alzheimer's properties [65]

Physical activity

Studies suggest that motor function impairment might precede the onset of clinical Alzheimer disease [66], but to what extent physical activity have a relation with cognitive decline disorders? Recent attention has been paid to the role of physical activity as a potentially protective factor against the risk of dementia [67]. In observational studies, subjects who are physically active often demonstrate less cognitive decline and lower risk of dementia than people who are inactive [67]. Moreover, a meta-analysis concluded that people who were not previously physically active showed improved cognitive function after exercising for as little as 4 months [68]

In a longitudinal study that examines the involvement between muscle strength and the incidence of Alzheimer disease in more than 900 persons initially free of dementia, the mean time of follow up was 3.6 years. Participants had structured evaluations of muscle strength, including 9 muscle groups strength testing in the upper and lower extremities, and axial muscle based on maximum inspiratory pressure and maximum expiratory pressure. Additionally, a detailed annual cognitive evaluations using 21 different tests was performed [69 70]. The number of participants who developed Alzheimer disease vs. who did not in different characteristics during the study were tabulated [69]. Individuals who developed AD were older, and showed decrease muscle strength in several muscle groups more than who remained free from the disease. As a result from the study, it was found that

participants in the highest decile of muscle strength were significantly less likely to decline cognitively over time compared to the lowest decile [69].

Conversely, physical activity might protect against cognitive decline. There is evidence of animals of neuroprotection from physical exercise [71]. The evidence of protection extends to humans. In a cohort study of 1880 elderly without dementia, living in New York, both diet and physical activity information were analyzed. The aim of the study was to find out the effect of both Mediterranean diet and physical activity on the risk of Alzheimer disease. Standardized neuropsychological measures were performed every 1.5 years. In addition to a weekly sum of various physical activities were reported and categorized due to type of activity [70]. The study showed that both higher physical activity and Mediterranean diet were independently associated with reduced risk of Alzheimer disease. Furthermore, as for the higher physical activity, the study observed a possible dose-response [70]. These data provide objective evidence that engagement in physical activity might be protective against cognitive decline and AD.

A population-based study of 1,500 people on aging and dementia in Finland found that those who engaged in leisure-time physical activity at least twice a week through middle age, carried half the risk of developing dementia and a 60 percent lower risk of developing Alzheimer's than did those who remained sedentary in their midlife. Although this relationship was seen in the entire population, the protective link was most pronounced in carriers of the ApoE ϵ 4 allele, suggesting that exercise carries some protective factor that can impede latent Alzheimer's pathology [72].

In the Canadian Study of Health and Aging, a prospective community-based longitudinal study of 4,600 elderly Canadians begun in the 1990s, researchers found that among women polled, the more frequent and intense the exercise reported, the lower the risk of dementia and Alzheimer's disease. A similar association was found in another study designed to learn about osteoporosis via health questionnaires given to six thousand women at six- and eight-year follow-ups. Nearly a quarter of the women who reported walking the shortest distances experienced cognitive decline, compared with only 17 percent of those who reported walking the greatest distances. Similarly, when researchers looked at the number of calories burned, the percent of women that burned the fewest calories who went on to develop cognitive decline was higher than the percent of women burning the most calories who went on to develop cognitive decline. Physical activity was assessed by a self-report that included such measures as distance walked and kilocalories used per week [73].

In another prospective U.S. study of dementia, researchers longitudinally assessed two thousand nondemented seniors in Seattle for an average of six years. Over the course of this period, 158 participants developed dementia, 107 of those developing Alzheimer's disease. After adjusting for age and gender-related risk, researchers found that people who exercised three times a week or more had an almost 40 percent risk reduction for developing Alzheimer's. The study relied on self-reporting, and covered a population that had already had a relatively high proportion of regular exercisers at baseline. Nevertheless, studies of nonexercising adults have come to similar conclusions, and the link between delayed onset of dementia/Alzheimer's disease and exercise confers it with extra value in the lives of elderly persons [74].

Conclusion

Dietary habits rich in essential nutrients and high physical activity are the main factors in constituting a healthy lifestyle. Therefore more investigations are needed to decide which lifestyle factor in particular is associated with reduced risk of AD. Limitations in every study

should be taken into consideration as they affect the results and conclusions, which make the replication of these population-based study results in clinical trials challenging [42]. Often, it is hard to reconcile the disparate findings from different studies as they yield different conclusions. This might be explained by differences in sampling, differences in covariate adjustments, or differences in length of follow-up.

Still unanswered is whether risk that is aggregated through health conditions, morphometrics, age, gender, and family history can be completely offset by diet, exercise and supplementation. There is a need to develop models of the risks for Alzheimer's disease and determine if the models can predict the data (posterior estimation). Risk assessment tools have been developed to estimate aggregate risk(75)(76) [Kivipelto 2006, Barnes 2009] but have not been applied prospectively in clinical trials to determine if they predict outcomes. Because longitudinal studies are costly, they routinely do not collect a broad array of risk factors, and can therefore not adjust the targeted risk factors or interventions for these unmeasured covariates. One way to reconcile this is to apply Hierarchical Bayesian methods. These methods make it possible to combine different data sets with different strengths and weaknesses, which would allow one to adjust for a much larger covariate vector of potentially influencing conditions. They also tolerate a wide range of missing data structures, which are a real problem in medical research, and they provide mechanisms for dealing with virtually any distribution that the data may have. This will important to do moving forward to factor in or factor out whether risks or healthy interventions affect treatment outcomes that are assessed *a priori*.

The association between high adherence to the Mediterranean diet and lower risk of Alzheimer disease is vital, and may be mediated by the combined effect of the consumption of some beneficial components, such as fish intake, fruits, and vegetables rich in antioxidants such as vitamin C, vitamin E and higher intake of unsaturated fatty acids. It is possible that Mediterranean diet with all its nutritional facts delays the decline in cognitive function specifically related to brain aging, but its effect on Alzheimer disease still uncertain. Although a decrease in muscle strength may represent a newly discovered risk factor for Alzheimer disease, theories of common pathogenesis may explain the loss of muscle strength and cognition in aging populations. The neurobiological association between AD and its risk factors are still unclear. Additional research is required to clarify their relationship.

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Figure 1. Docosahexaenoic acid (DHA) and its neuroprotective properties. Affect on amyloid plaque formation and aggregation, improves cerebral blood flow and reduces inflammation.