Increasing relative unsaturated fat intake to reduce Alzheimer's Disease risk

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Abstract

Alzheimer's Disease (AD) is a progressive neurodegenerative disorder, affecting almost 50 million people worldwide. AD is characterized by the accumulation of neurofibrillary tangles & amyloid plaques. Since AD is a disease mostly occurring in the elderly population, research is important as the population ages due to population growth. With the rise of studies linking dietary habits with disease prevalence over the past decades, dietary fatty acids (FAs) seem to play a role in multiple disease patterns. Here, unsaturated FAs are generally considered favorable from a health perspective, whereas saturated FAs are considered unfavorable. This thesis discusses a selection of studies directly relating AD with unsaturated FA intake, as well as dementia and cognitive function as a whole. Besides, we discuss variants of unsaturated FAs and how they may attribute to a lower risk of developing AD. These studies are supported by an analysis of possibly involved pathways, also related to comorbidities like diabetes and cardiovascular disease. A relatively high unsaturated FA intake, as well as a healthy balance with saturated FAs, may lower the risk of developing AD. Future research is necessary, as current views and studies are scarce and susceptible to confounding factors.

Contents

Introduction

Alzheimer's Disease (AD) is the most prevalent form of dementia worldwide, with almost 50 million estimated cases worldwide, making up about three-quarters of total dementia cases. It is characterized by irreversible degeneration of the brain, causing a progressive decline of memory and cognitive functions, eventually leading to death by total brain failure. Brain deterioration in AD is attributed to the formation of neurofibrillary tangles and amyloid plaques, spreading through the cortex as the disease progresses over the years.

Multiple studies have concluded that a high intake of saturated and trans-unsaturated fatty acids (FAs) have an opposite effect on the risk of developing AD when compared with (poly)unsaturated FAs (Kalmijn et al., 1997, Morris et al., 2003). These studies suggest a link between cognitive function, atherosclerosis, and thrombosis, the latter two often arising from complications with cholesterol mobilization.

Whereas the direct link between dietary FA intake and cognitive function has not been extensively researched, the impact of following a Mediterranean diet on cognitive function and dementia has. This diet has shown promising results in lowering the risk of dementia-associated disease (L. Wu & Sun, 2017), while positive health effects of this diet are all but limited to cognitive function. Although the Mediterranean diet consists of a multitude of dietary elements that have been positively associated with a healthy lifestyle, one of the main pillars of the diet is a high intake of unsaturated FAs via fish and olive oil consumption.

The extensively studied positive effect of the Mediterranean diet on cardiovascular diseases may indirectly be an explanation for or a correlative factor in the emergence of dementia. This correlation could be further supported by evidence of a protective effect of cholesterol-lowering statin drugs on cognitive deterioration in AD patients (Lin et al., 2015). Studies over the past decades have shown that obesity, diabetes, and high blood pressure are linked to a higher risk for developing AD. These are factors that are associated with lifestyle choices including dietary choices involving excessive sugar and saturated fat consumption, often combined with a lack of physical exercise.

Another possible pathway in this dietary intervention involving dietary FAs is an impairment of the blood-brain barrier. A decreased function of the blood-brain barrier leads to decreased Aβ transport from the brain to peripheral tissues (Cai et al., 2018). Several other negative effects of an impaired blood-brain barrier on cognitive function have been described, such as a dysfunctional neurovascular unit, which includes neurons, glial cells, and pericytes (Zenaro et al., 2017).

In this thesis, we will first discuss the pathology of AD and the composition of common dietary FAs. Next, we will review a selection of studies associating dietary FA intake with risk of AD development, complemented by research looking at dementia and diet implementation. These studies will be supported by providing an image of potentially involved pathways, also related to comorbidity. Lastly, we will discuss difficulties in research for this topic, and what future research could implement to gain a clearer perspective.

Characteristics of AD

AD is a neurodegenerative disorder, with patients displaying several cognitive and noncognitive symptoms during the progression of the illness. These symptoms may present themselves at the beginning of the pathology, but usually emerge in a later stadium. Patients with AD display a broad variety of symptoms, most commonly including personality change, affective disorders, psychotic characteristics, agitation, and apathy (Chung & Cummings, 2000). Both cognitive and noncognitive symptoms occur due to progressive damage to various parts of the brain. The two principal features of AD pathology in the brain are neurofibrillary tangles and amyloid plaques.

Neurofibrillary tangles & amyloid plaques

Neurofibrillary tangles are composed of abnormally paired fibrils, which form a helical structure by intertwining. The main component of these tangles is the *tau* protein, normally associated with microtubuli. The *tau* protein is abundant in particularly neurons of the central nervous system, in AD patients and healthy people alike. Within neurofibrillary tangles, however, the *tau* protein is abnormally phosphorylated. The dispersion of neurofibrillary tangles is relatively consistent across AD patients. Studies have shown a correlation between the dispersion and abundance of neurofibrillary tangles with the extent of dementia (Perl, 2010).

In comparison with neurofibrillary tangles, amyloid plaques are more specific for AD. These plaques mainly consist of β-amyloid protein (Aβ protein), which is derived from amyloid precursor proteins (APP proteins). The transmembrane APP proteins are cleaved into soluble derivatives, including Aβ proteins, which weigh in at around 4 kDa (Sisodia, 1992). In AD, these Aβ proteins accumulate to form amyloid deposits, eventually forming immature amyloid plaques containing damaged neurites. These plaques evolve in locations like the amygdala, hippocampus, and the frontal cortex. Mature plaques represent lesions containing necrotic material at the center, surrounded by macrophages and fibroblasts (McGeer & McGeer, 1995).

The most common genetic risk factor for the development of AD is the ε4 allele, which codes for apolipoprotein E4 (*APOE* ε4). More than half of the diagnosed AD patients possess this allele. The ApoE lipoprotein can occur in three versions, depending on the amino acids at the 112 and 158 positions. The risk for developing AD is about two to three times higher in individuals with a single *APOE* ε4 allele, whereas two *APOE* ε4 alleles increase the risk about 12 times (Michaelson, 2014). Neurofibrillary tangles and amyloid plaques contain deposits of the ApoE lipoprotein, where carriers of the *APOE* ε4 build up a significantly higher amount of ApoE (Hansen et al., 1994). Brain inflammation, one of the characteristics of AD, appears to be more pronounced in patients with the *APOE* ε4 allele. Anti-inflammatory medicine like NSAIDs reduces the risk of AD significantly in *APOE* ε4 carriers (Szekely et al., 2008).

Stages of AD

By localizing damaged neurons in deceased AD patients, the severity of the pathology can be evaluated. This has led to the identification of six stages of AD. In the first stage, small deposits of neurofibrillary tangles and amyloid plaque deposits can be identified in the trans-entorhinal cortex. Stage two envelops increased pathology in this region and the degeneration of the entorhinal region. These first two stages generally do not induce significant symptoms and are therefore considered preclinical.

The third identified stage of AD includes further degeneration of the entorhinal and trans-entorhinal regions, accompanied by mild alteration of the hippocampal formation. Further

breakdown and spread to the neocortical regions characterize stage four. In most AD patients, the first clinical symptoms arise in these stages. In stage five, the neocortex is destroyed, and in the final sixth stage, the breakdown process evolves to the sensory and motor regions. Due to the first stages providing minimal clinical symptoms, significant damage to the brain has already been facilitated before diagnosis (Shoghi-Jadid et al., 2002).

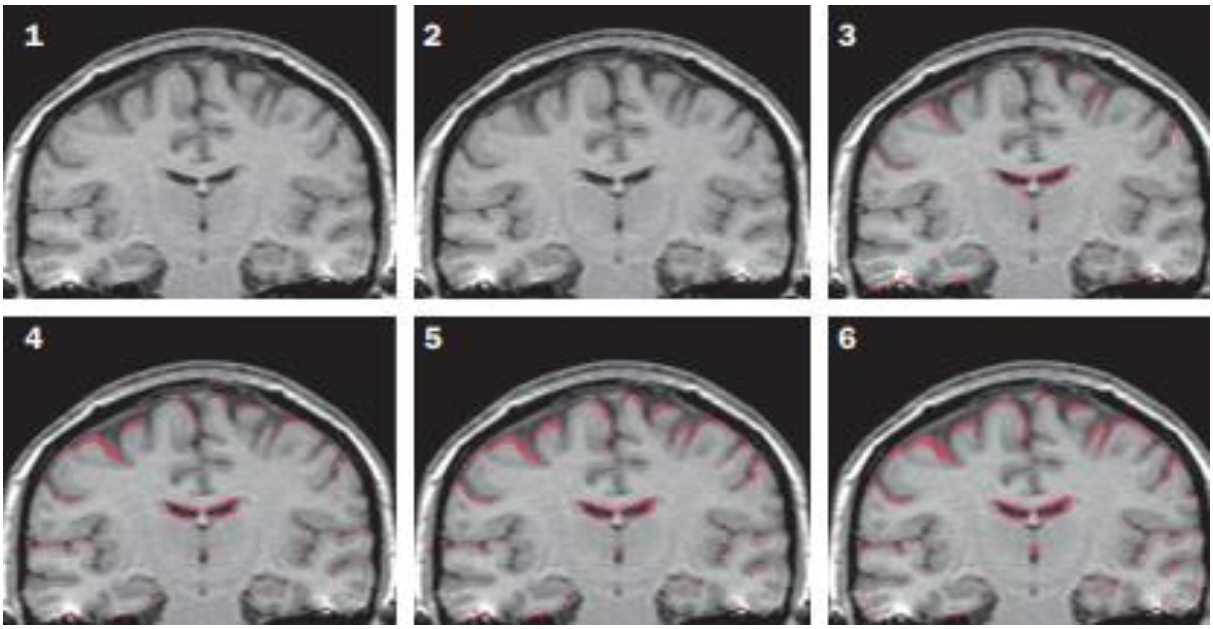

Figure 1: MRI scans from an initially nondemented patient developing AD. The scans have been acquired over a timespan of four years, with first dementia symptoms registered between scan 4 and 5. Note that the numbers do not correlate with the described six stages of AD (Fox & Schott, 2004).

Fatty acid composition

Dietary FAs can be divided into multiple groups. These groups are characterized by the presence of double or triple bonds in the structural composition of the FA. Triple bonds in FAs are less prevalent than double bonds, and more likely to be found in plants. Whereas monounsaturated FAs contain a sole double or triple bond, polyunsaturated FAs contain multiple. The position and configuration of the unsaturation determine key physical properties, like solubility and melting points (Cahoon et al., 1997). Saturated FAs are free from double or triple bonds and are usually in a solid state at room temperature. The lack of double or triple bonds makes stacking easier, leading to an increase in intermolecular interactions when compared to unsaturated FAs. Saturated FAs, therefore, tend to have higher melting points than unsaturated FAs (Lupi et al., 2016). Although they are mostly found in meat sources, saturated FAs are also abundant in some plant sources like coconuts, palms, and their respective oils.

Trans FAs are variants of unsaturated FAs that are formed by the addition of hydrogen atoms. This process is carried out by the food industry in order to solidify vegetable oils, which naturally occur as liquids. This solidification ensures that the end product has a longer shelf life and is more stable when used with deep-frying food. Usually, unsaturated FAs exist in a *cis*-configuration regarding the structural composition. During the hydrogenation of unsaturated FAs, the double bond(s) break, forming saturated FAs. However, incomplete hydrogenation can lead to an isomerization reaction, forming *trans*-configured unsaturated FAs. Intake of trans FAs has been extensively linked to adverse health effects, with a primary focus on cardiovascular disease (Mozaffarian et al., 2006;

Van De Vijver et al., 2000). For this reason, many countries have introduced legal policy to minimalize trans FAs intake.

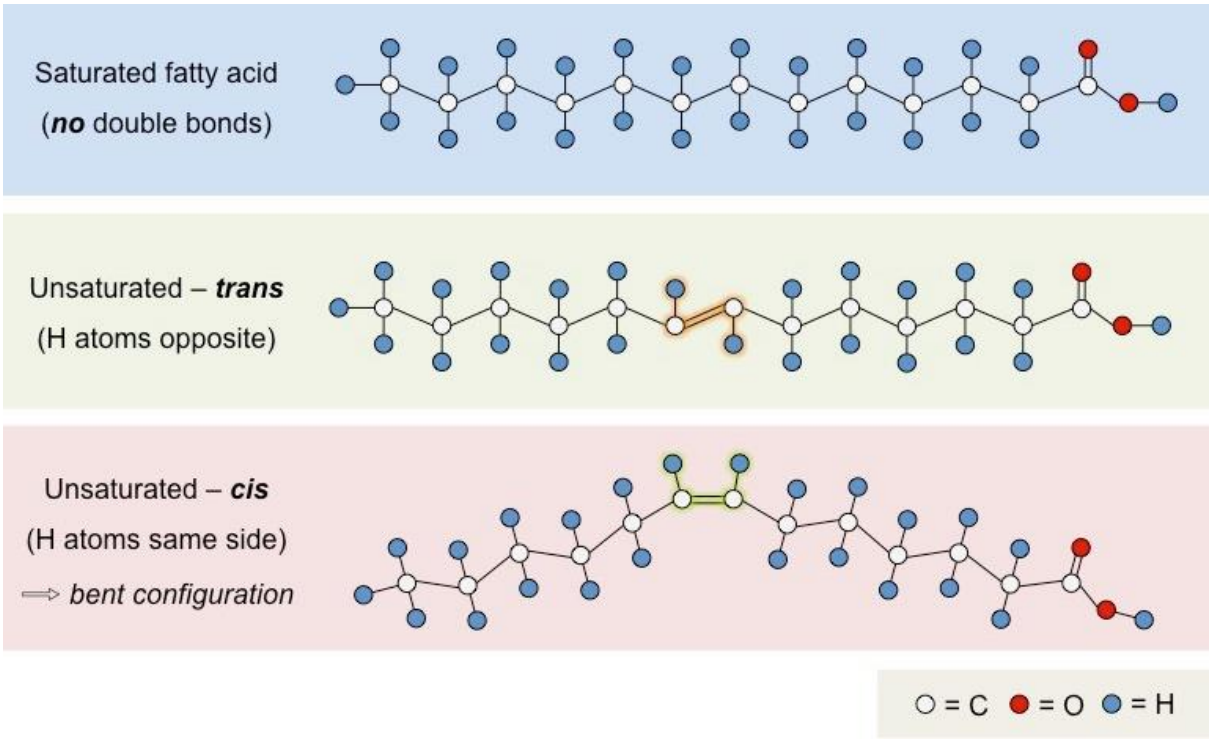

Figure 2: Visualization of the configuration of saturated FA, trans-unsaturated FA and cis-unsaturated FA (image retrieved from ib.bioninja.com.au).

Two variants of polyunsaturated FAs are essential, meaning humans require dietary sources for these FAs. These essential FAs consist of a-linolenic acid and linoleic acid, also named omega-6 FA and omega-3 FA respectively. Vegetable oils provide a large amount of essential FAs. Omega-6 FAs can mainly be found in oils like sunflower, corn, and sesame oil. Whereas vegetable oils like peanut oil and walnut oil are sources of omega-3 FAs, these FAs can also be found in oily fish and derivatives (Singh, 2005). Relatively high consumption of omega-3 FA has been linked to various positive health effects in disease research, which has been correlated to a shift in the ratio of a-linolenic acid and linoleic acid. These health effects, however, may vary considering specific diseases (Simopoulos, 2002).

Research related to unsaturated FAs

Alzheimer's Disease and dementia

Morris et al. (2003) investigated a direct link between specific types of dietary FAs and AD. 815 participants of 65 years and older without AD symptoms at baseline were assessed via a questionnaire. This questionnaire, based on the frequency of dietary habits, was evaluated for a mean of 2.3 years. After a mean follow-up of 3.9 years, a total of 131 participants were diagnosed with AD. Evaluation of the results showed that a high intake of saturated and trans FAs correlated with AD incidence. On the contrary, a high intake of omega-6 FAs and monounsaturated FAs correlated with a marginally significant decrease in AD incidence. Whereas vegetable fat consumption had a protective effect on AD development, the data showed that animal fat and dietary cholesterol were not associated with AD.

Coupled with this research, Morris et al. (2003-2) specifically investigated whether consumption of fish and omega-3 FAs would impact the risk of developing AD. They found that participants who ate fish at least once a week had a 60% decrease in AD incidence. Intake of omega-3 FAs had an inverse and linear association with risk of AD development. The latter effect, however, was only detectable among participants who possessed the *APOE* ε4 genotype. The protective association was profoundly noticeable when looking at omega-3 FA variant docosahexaenoic acid (DHA), which is abundant in fish. Parts of the human brain with high metabolic activity contain high levels of DHA.

A similar approach was applied by Kalmijn et al. (1997), who researched the association between FA intake and dementia among a larger pool of 5,936 nondemented participants. The research consulted data from the Rotterdam Study, which investigated a selection of chronic diseases in elderly people. Participants were at least 55 years at baseline and were assessed by a food frequency questionnaire. Food intake was screened at baseline and after a follow-up with an average of 2.1 years. During this follow-up, 58 (1.1% of total) participants became demented, of which 42 (72%) were diagnosed with AD. An increased risk for developing dementia was associated with high consumption of total fat and saturated fat, even more so for dementia with a vascular component. On the contrary, high fish consumption was inversely associated with incident dementia, once again linked to the high amounts of omega-3 FAs in fish. This effect was more evident for AD specifically.

Engelhart et al. (2003) did a follow-up to this research, now with a mean follow-up of 6.0 years. By now, of the 5,936 participants from the original study, 197 (3.7% of total) participants became demented, of which 146 (74.1%) were diagnosed with AD. From this follow-up, it was concluded that intake of monounsaturated FAs, polyunsaturated FAs, omega-3 FAs, and omega-6 FAs was not associated with AD. The study discusses the possibility of bias, due to conditions like cardiovascular disease and diabetes. These conditions are associated with both FA intake and the development of dementia. A second discussion point is that the research method, a diet-related questionnaire, may not reflect long-term intake of dietary FAs. Combining these two points, participants with comorbidity like cardiovascular disease may have adjusted their diet to reduce risk of escalation. The researchers, therefore, declared they could not draw resolute conclusions based on this study alone.

Conquer et al. (2000) took a more technical approach by performing a serum FA analysis between AD patients, patients with other dementias (OD), and control subjects. Of the 84 participants, 19 were diagnosed with AD, 10 with OD, and 36 with cognitive impairment without dementia (CIND). The other 19 participants belonged to the control group. Each participant donated a small amount of blood, which was then analyzed for total saturated FAs, polyunsaturated FAs, and monounsaturated FAs. Plasma phospholipid and phosphatidylcholine levels of DHA and total omega-3 FAs were lower in AD, OD, and CIND groups, as well as the omega-3/omega-6 FAs ratio. In the plasma phosphatidylethanolamine fraction of serum samples, total omega-3 FA levels were significantly lower in AD, OD, and CIND groups. Although not specifically for AD, this research demonstrates that low levels of plasma omega-3 FAs may pose as a risk factor for cognitive impairment and dementia. As opposed to what this study provided as hypothesis, low plasma DHA levels were not limited to AD patients alone.

Multiple of these studies found that higher intake of saturated FAs may also be linked to a higher risk of developing AD, next to the association between the intake of unsaturated FAs and a decrease in risk. In these studies, a relation between trans FAs and risk of developing AD seems debatable, with mixed results. This may also be a confounding factor for the associations with saturated FA intake. Omega-3 FA intake, the DHA variant in particular, and the ratio of omega-3/omega-6 FA intake show convincing results in all

of the studies where this was evaluated, albeit not for AD alone. More research after the specific link between unsaturated FAs, omega-3 FAs and AD will have to be conducted to draw any resolute conclusions.

Cognitive function

Whereas specific research for a direct link between unsaturated FAs and AD is scarce, multiple studies have investigated a correlation between unsaturated FA intake and cognitive function in humans. One of the difficulties these studies face is the duration of research, since adequate follow-ups tend to be longer and require frequent questionnaire updates from participants. On the other hand, animal studies for cognitive performance can be viewed as incomplete, due to the complexity of human behavior and the differences between the animal and human brain. For neurological disorders like AD and dementia, multiple screening instruments have been developed over the past decades. This provides a clearer insight for studies associating nutrients with risk and pathology of these neurological disorders.

Solfrizzi et al. (2006) investigated the connection between age-related cognitive decline and intake of unsaturated FAs in a follow-up study lasting 8.5 years. 278 participants from the larger Italian Longitudinal Study on Aging with a mean age of 73 years performed a dietary assessment and a neuropsychological evaluation. The dietary assessment consisted of a food frequency questionnaire, from which estimated variables were derived. This questionnaire was administered at a one-year interval. Cognitive function was evaluated with a Mini-Mental State Examination (MMSE), which covers variables like concentration, attention span, space and time orientation, and language components like verbal memory and constructive word usage. The MMSE was administered at baseline, after 41-54 months for the second survey, and after 96-109 months for the third survey. Results indicated that, with the use of a total energy intake model, high monounsaturated and polyunsaturated FA intake were significantly associated with less cognitive decline over time. This association remained firm when results were adjusted for confounding factors like age, BMI, sex, and total energy intake.

A different approach was taken by Okereke et al. (2012), who performed a four-year-long serial cognitive testing five years after dietary assessment. In this study, intake of the four main FA types (saturated, monounsaturated, polyunsaturated, and trans-unsaturated FAs) was related to cognitive performance. As opposed to the Solfrizzi et al. study, the sample size for this research was considerably bigger, featuring 6,183 female participants from the Women's Health Study in the US. Cognitive function was investigated by implementing two tests, consisting of the Telephone Interview for Cognitive Status (TICS) and the East Boston Memory Test (EBMT). Via these two tests, mainly memory performance and language components were assessed. Higher saturated FA intake correlated with higher global cognitive and verbal memory decline. On the contrary, higher monounsaturated FA intake was related to better cognitive and verbal memory decline. Total fat, polyunsaturated FA, and trans-fat intake showed no significant correlation with any cognitive trajectory researched.

Diet implementation

A great amount of research can be found regarding specific diets, of which several have shown promising results concerning disease. The Mediterranean diet is especially relevant for the covered subject, because of the implementation of specific macronutrients and their composition. This diet mainly features an abundance of plant foods, which contain mostly unsaturated FAs as opposed to saturated FAs. The primary source of fat in this diet is the usage of olive oil, which is rich in unsaturated FAs. Fish is consumed in moderate amounts, whereas the intake of (red) meat is minimized. Ideally,

adherence to this diet means a low (7-8% of total energy) consumption of saturated fats, as opposed to a relatively high intake of unsaturated FAs. The Mediterranean diet is mostly associated with a protective effect on cardiovascular disease.

To investigate a possible relation between adherence to the Mediterranean diet and AD, Nikolaus et al. (2006, 2007) performed double research for both the risk of developing AD, and mortality in patients with AD. Adherence to the Mediterranean diet was assessed via a score table with scores ranging from 0 to 9, with 9 resembling stricter adherence to the diet. 2,258 nondemented participants were followed with intervals of around 1.5 years, with a total mean follow-up of 4 years. The AD risk study concluded that higher adherence to the Mediterranean diet correlates with a significantly lower risk for AD development, with results remaining significant after adjustment for covariates. 192 of these subjects, who developed AD, were then assessed for mortality for the second study using the same Mediterranean diet adherence scores and intervals of 1.5 years. Over the course of the 4.4 years mean follow-up, 85 (44%) of the participants died. Once again, a protective effect of the Mediterranean diet was noticeable, with higher adherence correlating with lower mortality in AD patients. Once again, adjusting for covariables and the presence of baseline cardiovascular risk factors did not change the significance of the results.

Féart et al. (2009) conducted similar research in France, but the follow-up duration was notably greater. Also, this study examines dementia as a whole, instead of AD specifically. After two, four, and seven years after baseline, three follow-up examinations were performed from a pool of 9,294 participants. The same Mediterranean diet assessment Nikolaus et al. wielded in their dual research was used here, with scores ranging from 0 to 9. Cognitive function was assessed by using four tests, consisting of the MMSE, Benton Visual Retention Test (BVRT), Isaacs Set Test (IST), and the Free and Cued Selective Reminding Test (FCSRT). In this research, there was no significant association between participants who developed dementia (n = 99) or AD (n = 66) and their adherence to the Mediterranean diet. Besides, there was no significant relation between BVRT, IST, and FCSRT scores and Mediterranean diet adherence either. The only significant link found was between diet adherence and slower MMSE cognitive decline.

These studies provide contradictory results to some extent, which can be explained by a number of reasons. The Féart et al. study was carried out in France, whereas Nikolaus et al. performed their research in the United States. Diet composition and habits are different, as are the availability and usage of supplements which may not be included in the Mediterranean diet adherence score validation. This adherence score poses another problem, since diet is assessed on several large criteria with only zeroes and ones. This means that, when a participant scores either a zero or one, there is very little to no information about the quantity or preparation of the diet component. Besides, all individual pillars scored weigh equally, whereas different nutrients may vary widely in their contribution to any protective or detrimental effects on developing AD or dementia.

Pathways

APOE and cholesterol

Over the past decades, many studies have shown that saturated fats seem to elevate serum LDL cholesterol levels, whereas unsaturated fats have an opposite effect. High serum LDL cholesterol levels may lead to deposits on the vessel walls, posing a risk for cardiovascular disease in the long term. Statins are known to specifically intervene in this system, lowering serum cholesterol levels by reducing liver cholesterol production. In animal models, high cholesterol levels increase Aβ protein concentrations and may

increase *APOE* expression, indicating a correlation between serum cholesterol and AD pathogenesis (C. W. Wu et al., 2003).

Evans et al. (2004) studied the effect of total cholesterol levels on cognitive function and performance in 443 AD patients with and without the ε4 allele. Cognitive performance was assessed using the Alzheimer's Disease Assessment Scale, starting from baseline. They found that cognitive decline was most prominent in the AD patients group without the ε4 allele but with high cholesterol. Interestingly, AD patients with or without the ε4 allele but with normal cholesterol levels showed less cognitive decline. One of the possible reasons this study provides is that the ApoE 3 lipoprotein isoform has a higher binding affinity with cholesterol than the ApoE 4 isoform. The clinical trial period was relatively short however, with an analysis of 30 weeks.

Kivipelto et al. (2002) researched the association between *APOE* genotype, midlife blood pressure, total cholesterol levels, and AD development during a mean follow up of 21 years among 1,449 participants. This study, as opposed to the Evans et al. study, looked specifically at the development of AD in nondemented participants over a long trial period. The results once again showed that the ε4 allele was a risk factor for AD. However, elevated midlife cholesterol levels and systolic blood pressure appeared to be independent risk factors for AD as well, also after adjusting for confounding factors including the *APOE* genotype. This means that the correlation between possessing the ε4 allele and the development of AD seems to be unaffiliated with vascular risk factors.

Blood-brain barrier

The Aβ protein, produced in both the brain and periphery, is transported over the blood-brain barrier (BBB) and can be a cause of cellular stress, leading to neuronal dysfunction. Central nervous system deposition of Aβ protein is enhanced in AD. Since the Aβ protein is neurotoxic, an optimally functioning BBB is important as transport over the BBB regulates central nervous system concentrations of Aβ protein. Via the BBB, Aβ protein from the periphery enters the CNS and Aβ protein from the brain is cleared, both through receptor-mediated mechanisms (Deane et al., 2003). In a situation where clearance pathways are compromised, Aβ protein can accumulate in the brain and facilitate the formation of toxic Aβ protein variants and subspecies (Monro et al., 2002).

Diakogiannaki et al. (2008) studied the effect of saturated and unsaturated FAs on the endoplasmic reticulum stress pathway in β-cells, leading to their death. This effect was researched by exposing β-cells to the saturated FA palmitate and the monounsaturated FA palmitoleate. They concluded that saturated FAs increased β-cell apoptosis by activating components of a specific stress pathway of β-cells. On the other hand, monounsaturated FAs provide an antagonistic effect via regulation of kinase enzyme activity earlier in the same stress pathway of β-cells. Although this effect was specifically researched in β-cells, a similar mechanism may be occurring with the interaction between dietary FAs and endothelial cells of the BBB.

Takechi et al. (2008) demonstrated that rats fed with diets high in saturated FAs have increased circulating plasma Aβ protein levels. Their data suggest an association of Aβ protein with chylomicrons, which in turn may cause modulation of dietary FA metabolism. Furthermore, levels of enterocytic Aβ protein increase simultaneously with apolipoprotein B48. Consistent with the results of this research, Su et al. (1999) already demonstrated that animals infused with Aβ protein showed significant immunoglobulin G staining. This suggests an impairment of BBB integrity due to anomalous extravasation and accumulation of plasma proteins. Studies for a specific association between dietary FAs and BBB integrity in humans are otherwise scarce.

Inflammation

Several inflammatory pathways are involved in the development and pathology of AD. The complement pathway is activated by both amyloid plaques and neurofibrillary tangles (Rogers et al., 1992; Shen et al., 2001). This mainly concerns the classical complement pathway, but similar results have been found regarding the alternative pathway, mostly associated with amyloid plaques. Microglia produce complement proteins, and in AD cell cultures, microglia produced approximately twice as much complement protein C1q as nondemented cell culture microglia (Haga et al., 1996).

Both cytokine and chemokine pathways have been extensively researched in relation to AD. Practically all researched cytokines and chemokines are upregulated in an AD situation when compared to nondemented values. Cytokine TNF-α is one of the most prominently researched inflammatory cytokines and is elevated in AD serum, cortex, and glial cell cultures after Aβ protein exposure. TNF-α, however, has also been shown to have neuroprotective effects. Barger et al. (1995) showed a protective effect of TNF-α and TNF-β against Aβ protein toxicity. This involves a Ca2+ response to glutamate in neurons exposed to Aβ protein, which is suppressed in cell cultures first exposed with both TNF cytokines.

Kalogeropoulos et al. (2010) found that plasma unsaturated FA levels were inversely associated with inflammation and coagulation markers. Multiple inflammation markers, including interleukin-6 and TNF-α, were measured in 374 healthy participants. Besides the unsaturated FA effect, the ratio of omega-6/omega-3 FAs showed even stronger correlations with inflammatory markers. Even though this study found little effect of dietary FAs as opposed to plasma FAs, the latter still represents the dietary intake of FAs. In addition, Cintra et al. (2012) showed that unsaturated FAs corrected inflammation in the hypothalamus. This study was performed in diet-induced obese mice, but may be of significance for AD as well.

Comorbidity

Both a higher intake of unsaturated FAs and a lower intake of saturated FAs have been extensively linked to cardiovascular disease and diabetes, which are often associated with AD onset as well (Gillingham et al., 2011; Risérus et al., 2009). Multiple risk factors for cardiovascular disease, such as a disturbed cholesterol balance and hypertension, act as risk factors for AD as well. Due to the role of ApoE in both cholesterol metabolism and Aβ protein clearance, possession of the *APOE* ε4 allele may increase both incidence and severity of both AD and the named comorbidities (Martins et al., 2006).

Switching to a diet with higher relative unsaturated FAs and lower relative saturated FAs may, therefore, be protective in AD patients with cardiovascular disease or diabetes. Besides, a diet like this may lower the risk for developing comorbidity like this, as research linking dietary FAs to cardiovascular disease and diabetes is significantly more abundant and less indecisive in results. Storlien et al. (1996) reviewed an interaction between unsaturated FAs and insulin resistance in skeletal muscle cell membranes. They found that mainly omega-3 polyunsaturated FAs, as well as a high omega-3/omega-6 ratio, improves insulin function. In the KANWU study, Vessby et al. (2001) demonstrated that a decrease of saturated FA intake and an increase of unsaturated FA intake improved insulin sensitivity, but not insulin secretion. Additionally, a high fat intake overall (over 37% of total energy) nullified these results.

Research linking cardiovascular disease and AD is difficult, as criteria for AD diagnosis intrinsically exclude participants with clinical cardiovascular disease. For example, strokes have been associated with a higher risk of dementia, which is then labeled as post-stroke

dementia (Leys & Pasquier, 2012). This immediately complicates research linking stroke and AD. Nevertheless, Whitmer et al. (2005) managed to investigate multiple midlife cardiovascular risk factors in 721 demented participants. They found that risk factors smoking, hypertension, high cholesterol, and diabetes at midlife corresponded with a 20 to 40% increase in risk for the development of dementia. Besides, these risk factors manifest in a dose-dependent manner, and the presence of multiple risk factors causes them to reinforce each other.

Discussion

Although specific research associating unsaturated FAs and AD disease is scarce, the discussed studies provide a promising image of diet interaction with the risk of developing AD. Studies investigating a link between dietary components, composition, and neurological disorders like AD have mainly focused on human dietary habits. These studies often include food questionnaires in combination with at least one neurological or cognitive assessment for a specific pathology.

In the past decades, research has led to the rise of a large database of interactions between diet and diseases like diabetes and cardiovascular disease. The main difference between these diseases and AD is that AD has a significant effect on memory and cognitive function. This may affect and invalidate food frequency questionnaires, especially for participants in later stages of AD development. Besides, validation of dementia is more susceptible to subjectivity, even when using the same assessment test. This makes a large participant pool and a long follow up crucial for reliable results.

On the other hand, animal studies for dementia and AD are complicated to match up with human studies, as animal behavior is not comparable to the complex human set of behaviors. This is especially true for the difference of impairment in demented animals and humans. Molecular research in animal models appears to come closer, but faces its own problems. For example, mice carry different Aβ precursor proteins and subsequent processing proteins. Besides, as animal models usually have a favorable genetic background for certain aspects, their behavior may be impossible to attribute to certain AD symptoms.

To gain a more detailed perspective of the interaction between AD development risk and dietary FAs in particular, research should focus on these parameters. Future studies have to keep the aforementioned large participant pool and long follow up in mind. Additionally, as many confounding factors as possible should be ruled out, preferably consulting nondemented helping hands to keep track of dietary habits and filling out the food frequency questionnaires. Furthermore, a better picture of the similarities between the animal model and human AD development and reliability of research must be obtained in order to make animal studies susceptible to human implementation.

The studies mentioned in this thesis show different yet promising results for the multitude of unsaturated FAs. Both monounsaturated and polyunsaturated FAs seem to have beneficial effects on the risk of AD development. Likewise, omega-3, omega-6, and the ratio between these two seem to be of importance. Mainly studies involving the Mediterranean diet show that a variant of omega-3, DHA, either improves cognitive function or slows impairment in both demented and nondemented participants. Therefore, specific research for these dietary FAs may provide new insights into AD development risk and AD pathology.

Lastly, a clearer picture of the involved pathways in combination with dietary FAs would improve the reliability of studies associating diet with AD. The cholesterol pathway, blood-brain barrier, and inflammation all seem to act on the risk of development and

pathology of AD. This effect seems to be greater for people possessing an ε4 allele. The interaction of this allele, pathways, and risk for AD development must be examined further to draw more accurate conclusions. All in all, a diet containing a healthy ratio of unsaturated FAs and saturated FAs has beneficial health effects overall. Adherence to a diet like this, especially in midlife, may be key to maintaining a healthy lifestyle and minimizing risks of developing AD and other diseases.

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