# The influence of dietary fat intake on Alzheimer's Disease

By
Maaike van der Meulen

THESIS

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Supervisor:
Dr. Ate S. Boerema

# Abstract

Alzheimer's disease (AD) is a progressive neurodegenerative disorder with two pathological hallmarks: Amyloid β plaques and neurofibrillary tangles. AD is characterized by a loss of memory and a loss of other cognitive functions. Because of the increase in age of the population, the number of people with AD is expected to double every 20 years. Means of prevention are needed. A healthier lifestyle is a possible target for reducing the risk of developing AD.

The intake of saturated fatty acids and trans fatty acids has been associated with an increased risk of AD. The intake of unsaturated fatty acids, however, has been associated with a reduced risk of AD. Although not all studies found these associations, a trend is clear.

Possible mechanisms for this associations include the change of LDL-cholesterol and HDL-cholesterol levels, glucose dysregulation, neuronal inflammation and oxidative stress. Cholesterol possibly plays a role in Aβ production and deposition. High-fat diet contributes to a decreased uptake of glucose in the brain, which is a factor in cognitive decline. High fat intake also damages the integrity of the blood brain barrier. This induces neuronal inflammation which leads to cerebral damage.

Heart disease and diabetes have also been associated with an increased risk of AD, while also being associated with dietary fat intake. Several explanations have been proposed. Both diseases are associated with hypertension, which has a direct effect on the risk of cerebrovascular diseases and thus dementia. An association with cholesterol has also been found in both diseases.

A healthier lifestyle by reducing the saturated fatty acid intake and replacing the saturated fatty acids with unsaturated fatty acids might be a good target for reducing the risk of developing AD.

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# Preface

In 2015 46.8 million people worldwide suffered from dementia and this number is expected to double every 20 years. In Europe alone there are already an estimated 10.5 million people suffering from dementia. Dementia brings many costs along with it. In 2015 the estimated cost of dementia worldwide was 818 billion US dollars (Prince et al., 2015). Means of prevention of dementia are needed.

Alzheimer's Disease (AD) is the most common form of dementia. It represents 60% to 80% of the cases (Cummings & Cole, 2002). Factors like old age, genetic factors, obesity, family history and diabetes are risk factors for developing AD (Bendlin et al., 2010). Several studies have shown that certain lifestyle and dietary factors are associated with the risk of AD (Fratiglioni, Paillard-Borg, & Winblad, 2004; Scarmeas et al., 2009). Dietary fat composition has also been found to be an important factor for diabetes and heart disease, which are associated with AD (Appel et al., 2005; Furtado et al., 2008). This could be a possible target for the prevention of AD.

In this thesis the results of several studies are shown to provide evidence for the association between dietary fat intake and the risk of AD. Furthermore several mechanisms are mentioned to explain this association. Diseases like diabetes and heart disease have also been associated with dementia. These diseases will be discussed. The purpose of this thesis is to verify whether a healthy lifestyle is of any influence on the prevention of AD.

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# Chapter 1
# Background

*1.1 Pathology of AD*

AD is an irreversible progressive neurodegenerative disorder, which is characterized by a loss of memory and a loss of other cognitive functions like motor skills and is also characterized by personality changes (Bendlin et al., 2010). The pathology of AD, however, starts much earlier than the symptoms. There are two main pathological features: amyloid plaques and neurofibrillary tangles (NFTs).

NFTs are associated with hyperphosphorylation of tau protein. This protein is present in high concentrations in neurons, astrocytes and oligodendrocytes to link microtubules together. Hyperphosphorylation of tau protein is the reason for the aggregates inside the neuronal cell body.

Amyloid plaques are formed by Aβ-peptides. Aβ-peptides come from amyloid precursor protein (APP). APP can be cleaved by β and γ secretase in the amyloidogenic pathway. APP can also be cleaved in a nonamyloidogenic pathway by α secretase. APP is then cleaved within the Aβ domain, thus Aβ-peptides are not formed correctly and cannot aggregate to amyloid plaques (Grimm et al., 2012).

Amyloid plaques and neurofibrillary tangles contribute to neuronal death, which results in a loss of connections within the brain. Initial damage takes place in the hippocampus and spreads as the disease progresses.

APOE ε4 is a gene located on chromosome 19 that is highly associated with an increased risk of AD. Though it is already present for 15% of the general population, its frequency rises to 40% in patients with AD (Corder et al., 2008). APOE ε4 plays a role with the absorption of cholesterol in intestine and is associated with higher plasma cholesterol levels (Corbo & Scacchi, 1999). Cholesterol in turn forms the core of the neuritic plaques typical for AD (Luigi Puglielli, Tanzi, & Kovacs, 2003).

*1.2 Fat metabolism*

When fats are being metabolized, they assemble inside intestinal epithelial cells into chylomicrons. These chylomicrons enter the venous circulation where lipoprotein lipase converts them to free fatty acids and glycerol to be used as energy. The chylomicron remnants are then taken up by the liver to be metabolized. These remnants consist of, among others, cholesterol. Cholesterol can be converted into bile salts. When this cholesterol is not converted into bile salts, it forms a complex with newly synthesized cholesterol and fatty acids and is then packaged in lipoprotein complexes to be secreted into the blood.

These lipoprotein complexes differ in amounts of cholesterol, triglycerides, apoproteins and phospholipids. When the complexes contain more proteins, they get heavier. These complexes can vary from low-density lipoprotein (LDL) to high-density lipoprotein (HDL). LDL contains ApoB,

which can bind to receptors which can in turn bring LDL into the cell. HDL contains ApoA, which helps with cholesterol uptake by the liver and other tissues (Silverthorn, 2014). In conclusion, LDL-cholesterol is stored in cells, thus it is not healthy in high quantities. HDL-cholesterol helps with the uptake and deterioration of LDL-cholesterol, thus is a much more healthy variant than LDL-cholesterol.

*1.3 Differences in dietary fat*

Fatty acid composition is determined by the number of double or triple bond in the fatty acid chain, the position of unsaturation in the fatty acid chain and the configuration of the hydrogen atoms (Morris et al., 2003). Fatty acids can both be found in animal and plant sources.

Saturated fatty acids are solid at room temperature and have no double bonds (Morris et al., 2003), thus they are saturated with hydrogen. These fatty acids are predominantly found in meat and dairy. They tend to elevate LDL-cholesterol.

Unsaturated fatty acids have one (mono) or more (poly) double bonds and are predominantly found in fruits, vegetables, nuts and fish. Unsaturated fatty acids elevate HDL-cholesterol.

The two essential fatty acids, a-linoleic acid (18:2 n-6) and a-linolenic acid (18:3) n-3), are polyunsaturated fatty acids. The essential fatty acids are the fatty acids the human body cannot make itself, but are needed to maintain a good health. These fatty acids are needed for the absorption of vitamins E, A, D, K and the carotenoids. They are found among other things in seeds and vegetable oil (Morris & Tangney, 2014). These compounds might be important for brain health. Docosahexaenoic acid (DHA; 22:6n-3) is a polyunsaturated acid which is found predominantly in fat fish like salmon. Though the human body can make DHA itself by processing α-linolenic acid, it is in such low concentrations that it can be seen as an essential fatty acid. DHA is found in brain grey matter (Morris, Evans, Bienias, Tangney, Bennett, Wilson, et al., 2003).

Trans fatty acids are unsaturated fatty acids which are hydrogenated to improve the shelf-life of products, like margarine. They are also present in natural food products as a result of bacterial fermentation in ruminant animals. However, most of the dietary intake of trans fatty acids are artificially made. These fatty acids increase LDL-cholesterol and decrease HDL-cholesterol and accumulate in the membranes of cells (Mozaffarian, Aro, & Willett, 2009). Trans fatty acid consumption has been low in European countries with an even historically low consumption in the Netherlands (Michels & Sacks, 1995).

# Chapter 2

# AD and dietary fat intake

*2.1 In vitro & animal studies on the association between AD and dietary fat intake.*

Grimm et al. (2012) conducted a research to investigate the influence of trans fatty acids on AD. They used cell cultures to look at the effects of trans fatty acids on the processing of APP and their impact on AD. They found that the intake of trans fatty acids increased amyloidogenic APP and decreased nonamyloidogenic APP compared to the intake of unsaturated fatty acids, which resulted in an increased production of Aβ. They also found that trans fatty acids increased Aβ aggregation and oligomerization.

Oksman et al. (2006) directed a research on the influence of dietary lipids on accumulation of Aβ in the brain of mice. These mice followed different kinds of diets, varying in saturated fatty acids, polyunsaturated fatty acids and cholesterol contents for three to four months. They found that even the smallest variations in a diet could have an impact on Aβ accumulation. They found greater concentrations of Aβ in a 40% saturated fatty acids diet, typical for a Western diet, compared to a soy oil-based diet. They also found that a diet supplemented with DHA decreased Aβ levels compared to a soy oil-based diet. But DHA did more than that: it also decreased the number of activated microglia in the hippocampus and increased the explorary activity of the mice, but did not improve their performance on the water maze, made to test spatial learning.

Winocur & Greenwood (2005) conducted multiple studies using rat models. They looked at the cognitive function of the rats while on a high fat diet for three months. The rats on a high fat diet (20 % saturated fat) did significantly worse on all the tests, including long-term memory tasks and spatial memory tasks. Interestingly, they also found impairments in the rats on a high unsaturated fat diet.

Gamoh et al. (2001) investigated the effect of DHA on spatial memory in aged rats. They did this by performing a radial arm maze task. The rats were fed 300 mg/kg DHA per day for ten weeks or were just fed the vehicle alone. When the rats were fed DHA the rats significantly made less errors in the test. They also did a lipid peroxide (LPO) assay in the hippocampus, which is representable for cell damage. They found that a diet supplemented with DHA decreased LPO levels.

Calderon & Kim (2004) looked at the effect of DHA in neurite growth in hippocampal neurons. They looked at rat embryonic hippocampal primary cultures. When DHA was added to the medium the population of neurons increased, the neurite per neuron was longer and had more branches. Their conclusion was that DHA might improve cognitive functions.

A lot of research has been done to investigate the effect of fatty acids on AD in animals and in culture. One general conclusion could almost always be drawn: the animals which were on a high-saturated fat diet or a high trans fatty acid diet did significantly worse on cognition tasks and they formed more Aβ aggregation compared to animals on an unsaturated diet. This suggests that saturated

fatty acids increase the risk of AD. DHA decreased Aβ aggregation, suggesting that DHA might decrease the risk of AD.

A lot of behavioural studies have been done on animals following an unsaturated fatty acid diet or a more specific diet, like a DHA diet. Many studies also looked at the brain functioning of animals or cultures getting unsaturated fatty acid, but a direct link to AD is not clear. The studies do show a promising trend of improved cognitive functions and a better brain functioning.

*2.2 Human studies on the association between AD and dietary fat intake.*

Laitinen et al. (2006) did a population-based study with 1449 participants over 21 years, where the participants reported their spreads and milk products. The data they got were then corrected for demographics, subtypes of fats, vascular risk factors and disorders and ApoE genotype. They found that the intake of polyunsaturated fatty acids decreased the risk of dementia, while the intake of saturated fatty acids increased the risk of dementia. They also found that these associations were greater in APOE ε4 carriers. Their diet data is possibly, however, not representable for the whole diet of the participants. Despite this fact, this study is interesting because of the long follow-up time of 21 years. Many studies have a follow-up time of three to six years. In these studies, it is not a hundred percent solid if a diet consisting of a lot of saturated fatty acids might be a consequence or a cause of AD.

Luchsinger, Tang, Shea, & Mayeux (2002) looked at the caloric intake of 980 elderly individuals (65+) which did not show signs of dementia at the baseline. They also looked at the daily intake of carbohydrates, fats and protein. The research group was then divided in quartiles of caloric intake. After 4 years a follow-up was done. In the quartile with the highest caloric and fat intake an increased risk of AD could be found. An association between ApoE ε4 and a higher risk of AD could also be noticed.

Another interesting study is the Rotterdam study (Kalmijn et al., 1997), because of the high amount of participants they used (N=5395). The participants, which were 55 years or older at baseline, filled in a frequency questionnaire and they were continuously monitored for the incident of dementia. After a follow-up of 2.1 years a correlation between saturated fatty acid intake and AD incidence was found. They also found an inverse relation between fish consumption, which has DHA in it, and the prevalence of dementia. Interestingly, after a follow-up of 6 years, these correlations were not found anymore (Engelhart et al., 2002). One of the multiple explanations this study suggests for their findings is the occurrence of a bias. This study excluded participants with cardiovascular disease. It might be that the higher intake of saturated fat is associated with AD only in combination with a cardiovascular disease. This theory will further be discussed in chapter 4. Furthermore, they explained a possible reason for the difference in their two studies. The study with a follow-up of 2.1 years had a lower incidence of AD, which might be a reason for a bias.

More cohort studies have been done (Morris et al., 2003a; Morris et al., 2003b), showing an association between saturated fatty acid intake and risk of AD and a reverse association between unsaturated fatty acid intake and risk of AD. The Rotterdam Study did not show these results, though they are the biggest cohort study done to this day. A systematic review was done by Barnard et al. (2014) about these cohort studies and studies which are not mentioned in this thesis. Saturated fat intake was associated with risk of AD in three of the four studies, while the other study suggested an inverse association. Saturated fat intake was also associated with dementia, MCI and cognitive decline in some, but not all studies. They did not find a clear association between trans fat intake and dementia.

The Framingham Heart study looked at the effect of DHA on the risk of AD (Schaefer et al., 2006). 1137 participants were asked to fill in a questionnaire and levels of DHA were assessed. Participants who did not have dementia were followed for ten years. They found that not only did fish intake reduce the risk of heart disease, it also decreased the risk of AD with 48%. When participants had a high fish intake, their DHA levels were also elevated.

A lot of cohort have been done in different countries. Most of these studies found an association between saturated fatty acid intake and risk of AD and an inverse association between unsaturated fatty acid intake and risk of AD. It is also interesting to see that the results became even more significant in ApoE ε4 carriers. The intake of DHA seems to decrease the risk of AD. It is noticeable, however, that most studies used individuals that were 55 years or older. It would be interesting to see studies that followed individuals earlier on. This will probably be done in the future, as the participants of studies like LifeLines get older and start to develop dementia (Klijs et al., 2015).

# Chapter 3
# Possible mechanisms

*3.1 Cholesterol*

Saturated fatty acids increase LDL-cholesterol levels, while unsaturated fatty acids can decrease LDL-cholesterol levels. Cholesterol might play a role in AD risk. It has been speculated that cholesterol might play a role in Aβ production and deposition (Puglielli et al., 2001). There is, however, a difference in intracellular cholesterol and circulating cholesterol. It might be that intracellular cholesterol regulates Aβ production by modulating the secretases that cut APP. High concentrations of cholesterol increase γ-secretase activity and thus promote the amyloidogenic pathway, which results in an enhanced release of amyloidogenic Aβ. Low intracellular cholesterol, however, promotes the non-amyloidogenic pathway, which decreases Aβ deposition (Ehehalt, Keller, Haass, Thiele, & Simons, 2003).

The genetic factor APOE-ε4 is involved in blood cholesterol transport (Puglielli et al., 2003). APOE ε4 carriers have higher LDL concentrations and higher plasma total compared to non-carriers (Bennet et al., 2015). As mentioned before, APOE ε4 is one of the risk factors of AD.

The role of cholesterol in AD risk is further supported by studies claiming statin drugs, which are cholesterol-lowering, are associated with reduced AD risk. A meta-analysis was done by Song et al. (2013). They included the Rotterdam Study and six other big cohort studies. They found that the use of statins could reduce AD risk with an average of 62%. There was only one problem: in the Rotterdam study other cholesterol-lowering drugs did not give the same effect as statins (Haag, Hofman, Koudstaal, Stricker, & Breteler, 2009). This might suggest that the statins work beneficial for AD risk via another mechanism.

*3.2 Glucose dysregulation*

Winocur and Greenwood (2005) gave an alternative mechanism which might be involved in AD risk. A high-fat diet contributes to insulin resistance and decreased glucose uptake in the brain. This impaired glucose regulation is already a factor in the cognitive decline in normal aging, but also in type-2 diabetes. Winocur and Greenwood have tried to see if this was also the case for cognitive decline because of a high-fat diet. They put young adult rats on high-fat diets, including saturated fatty acids and unsaturated fatty acids. When the rats on a high-fat diet had cognitive impairments, they injected them with glucose (100 mg/kg). Interestingly, glucose treatment improved the performance of the rats significantly in both high-fat groups. This suggests that a high-fat diet indeed leads to a glucose dysregulation, which in turn worsens the cognitive abilities.

*3.3 Oxidative stress and inflammation*

Previously an association has been made between neuronal inflammation and AD (Holmes, 2013; Zlokovic, 2008). Takechi et al. (2013) suggest a possible mechanism via the alteration of the blood brain barrier by saturated and trans fats. They looked at the effect of dietary fat on the blood brain barrier in mice. They found that high fat diets decrease the integrity of the blood brain barrier. Mice which were fed a high saturated diet showed signs of cerebrovascular inflammation. Though it is unclear how this mechanism precisely works, some pathways have been suggested.

Morgan (2009) suggested that it might be because of the toxicity of the saturated fatty acids. This toxicity is a consequence of an endoplasmatic reticulum dysfunction and disturbances in protein processing. This toxicity could then induce damage. Patil et al. (2006) provided evidence that this could also be the case in the brain. They found that saturated fatty acids induced region-specific cerebral damage. This was because of the higher fatty acid-metabolizing capacity of astroglia in the cortex.

Another possible pathway would be an antagonistic function of unsaturated fatty acids on stress pathways (Diakogiannaki, Welters, & Morgan, 2008). This could lead to an anti-apoptotic environment. In the study of Diakogiannaki et al. they also found that saturated fatty acids promoted stress pathways, thus promoting apoptosis. Though this study was done on β-cells, this could also be the case in the brain.

# Chapter 4

# Associations between dietary fat, other diseases and AD

*4.1 Associations between dietary fat, heart disease and AD*

Abnormal plasma lipids are hallmarks for atherosclerosis and coronary heart disease. LDL-cholesterol is the most prominent hallmark. Oxidized LDL-C can be taken up by macrophages and that can lead to the forming of atherosclerotic plaques inside blood vessels. But also low HDL-C levels can be a predictor of heart disease (Silverthorn, 2014). As said in chapter 1, (un)saturated fatty acids influence the LDL and HDL levels. Indeed, dietary intake of saturated fatty acids and trans fats have been associated with coronary heart disease. Replacing saturated fatty acids with unsaturated fatty acids gave a decrease in risk of coronary heart disease, because of a reduction in LDL levels (Woodside, Mckinley, & Young, 2008).

Hypertension has been associated with dementia, specifically in midlife (Qiu, Winblad, & Fratiglioni, 2005). As is obesity (BMI > 30) at midlife, the risk of AD three folds then (Whitmer, Gunderson, Quesenberry, Zhou, & Yaffe, 2007).

The Cardiovascular Risk Factors, Aging, and Dementia (CAIDE) study have found that an increased risk of vascular diseases at midlife could predict AD 20 years later (Kivipelto et al., 2006). They conducted a research determining the most important predictors of AD. They took into account: Body Mass Index (BMI), systolic and diastolic blood pressure, smoking status, total cholesterol levels and level of activity. The most predictive factors were hypertension, cholesterol levels and obesity.

Risk factors of coronary heart disease, such as hypertension and hypercholesterolemia, can lead to hypoperfusion, ischemia and cerebrovasulcar disease. This influences the progress of dementia (Gorelick, 2004). People who had a stroke in the past have a 3.5 to 6 times greater chance of developing dementia than people who did not have a stroke (Hénon, Pasquier, & Leys, 2006).

*4.2 Associations between dietary fat, diabetes and AD*

Ohara et al. (2011) conducted a Japanese cohort study to investigate a possible association between glucose tolerance and risk of dementia. With a total of 1017 subjects aged 60 years and older a 75 grams oral glucose tolerance test was done. After a follow up of 15 years they found that diabetes was a risk factor for all types of dementia, but also for AD and vascular dementia specifically. What was very interesting in this study was the detailed examination. The subjects underwent neuroimaging and post-mortem autopsy so that the type of dementia could be specified.

Ohara et al. (2011) suggested some possible mechanisms. As was described above, hypertension has been associated with dementia. Diabetes seems to increase multiple cardiovascular risks, including hypertension.

Another mechanism is the change in insulin metabolism which might result in insulin resistance and therefor hyperinsulinemia (Kendler et al., 1992; Luchsinger et al., 2004; Ott et al., 1999). Insulin is an antagonist for Aβ, as they both compete for insulin degrading enzyme (IDE). In principal is IDE the regulator of Aβ in neurons and glial cells. When a larger amount of insulin is present in the body because of hyperinsulinemia, insulin can cross the blood brain barrier and thus impede the amyloid clearane (Farris et al., 2003).

Peila et al. (2002) also did a population-based cohort study using 2574 subjects. They found similar results as the study of Ohara et al. Interestingly they also found that carrying the APOE ε4 allele increased the strength of the association between diabetes type 2 and AD.

Another study looked at the influence of dietary fat on cognitive decline in older adults with diabetes (Devore et al., 2009). They followed 1486 subjects with type 3 diabetes for two years and assessed their dietary fat intake. They found that lower intakes of saturated and trans fats reduced cognitive decline. A higher intake of polyunsaturated fat also led to a reduction in cognitive decline.

# Epilogue

The association between saturated fatty acids and trans fatty acids and risk of AD has been shown in multiple studies, but not every study got the same results. A clear trend can, however, be seen: saturated fatty acid intake and trans fat intake increase the risk of AD, while unsaturated fatty acid intake decrease the risk of AD. How the saturated fatty acids and the trans fatty acids influence AD is not sure, but several mechanisms have been presented. Not one mechanism is solely responsible for the association.

A hypothesis could be that all the suggested mechanisms partially contribute to the association. Studies have mostly focused on just one mechanism. Further research is needed, which could take in mind the interaction of multiple mechanisms. It would also be interesting to see a further dissociation between monounsaturated fatty acids, polyunsaturated fatty acids, long-chain saturated fatty acids and short-chain saturated fatty acids to see if further dissociations might have an even bigger effect.

Overall a healthier lifestyle is key to healthier aging. Not only is the risk of AD reduced, the risk of diabetes, heart disease and several other aging diseases can be reduced significantly. To achieve this, a better understanding of what a healthy lifestyle consists of is needed and clear information is needed towards the public. At this moment there's a lot of confusion concerning different types of diets. A better guideline is needed, but needs to be backed up with good research.

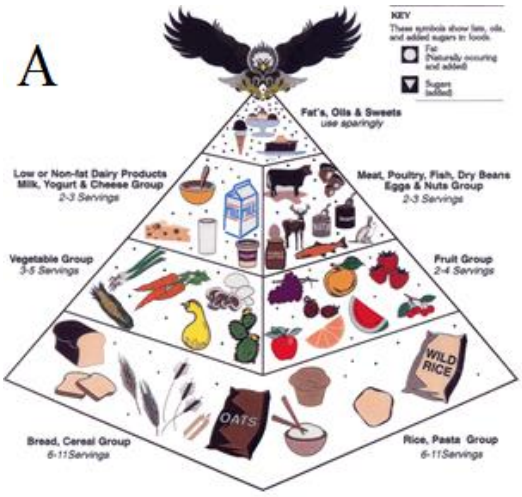



Figure 1a: The American food pyramid states that sweets, fats and oils are to be used sparingly. They have put saturated fatty acids and unsaturated fatty acids in one category, while their structure and health advantages are completely different. Retrieved from www.nativevillage.org

Figure 1b: 'De Schijf van Vijf' is the Dutch guideline concerning the amount of food groups that should be eaten. This guideline still suggests the use of trans fatty acids and does not put unsaturated fatty acids in a different category. Retrieved from www.schijf-van-vijf.nl

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