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Dietary fat composition and dementia risk

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Abstract

This is a qualitative review of the evidence linking dietary fat composition to the risk of developing dementia. The review considers laboratory and animal studies that identify underlying mechanisms as well as prospective epidemiological studies linking biochemical or dietary fatty acids to cognitive decline or incident dementia. Several lines of evidence provide support for the hypothesis that high saturated or trans fatty acids increase the risk of dementia and high polyunsaturated or monounsaturated fatty acids decrease risk. Dietary fat composition is an important factor in blood brain barrier (BBB) function and the blood cholesterol profile. Cholesterol and BBB function are involved in the neuropathology of Alzheimer's disease (AD), and the primary genetic risk factor for AD, APOE- ϵ 4, is involved in cholesterol transport. The epidemiological literature is seemingly inconsistent on this topic but many studies are difficult to interpret because of analytic techniques that ignored negative confounding by other fatty acids which likely resulted in null findings. The studies that appropriately adjust for confounding by other fats support the dietary fat composition hypothesis.

Keywords

Fatty acids; Alzheimer's disease; Dementia; Cognitive decline; Diet; Saturated fats; Trans fats; Polyunsaturated fats; Monounsaturated fats

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1. Introduction

Dietary fat composition has been demonstrated to be important in the prevention and treatment of cardiovascular diseases and diabetes, conditions that have also been implicated as risk factors for dementia (Appel et al., 2005; Furtado et al., 2008; Gadgil et al., 2013). Therefore, it would appear reasonable that at the very least, dietary fats would impact the brain through their effects on cardiovascular conditions. This review describes the evidence to date in support of dietary fat composition as a risk factor in the development of dementia and will include laboratory studies, animal models, and prospective epidemiological studies. Whereas animal and laboratory studies are emerging that suggest several biological mechanisms underlying the relationship of fat composition to dementia risk, the epidemiological evidence is inconsistent. The study of diet is complex and presents a number of analytic challenges. Historically, the field of nutrition has devoted limited attention to neurodegenerative diseases. Thus, a number of studies have used nutritionally unsophisticated analytic approaches that make it difficult to interpret the study findings. To give context to this discussion, we first provide brief descriptions of the different types of dementia and of dietary fats followed by a critical review of the evidence.

1.1 Dementia and Alzheimer's disease

Dementia is an umbrella term for diseases that affect mental abilities severely enough that the ability to perform tasks of daily living is impaired (American Psychological Association, 2000). Alzheimer's disease (AD) is the primary form of dementia and represents 60 to 80% of cases (Bennett and Evans, 1992). Memory loss is central to AD, along with impairment in one or more other cognitive abilities, i.e., visual perception, language ability, reasoning, or attention (Bennett and Evans, 1992). Some of the more common forms of dementia are vascular dementia, dementia with Lewy bodies, and mixed dementia. Few studies have reported on the dietary relationship to vascular dementia or other rare dementia diseases because of the limited number of incident cases in cohort studies. Because the diagnosis of dementia and its various forms is expensive and susceptible to bias, studies that relate risk factors to a decline in cognitive abilities are important additions to the literature. These types of investigations allow for much larger populations to be studied at a fraction of the cost of clinical disease evaluations. Further, they have the advantage of being less prone to bias and allow for the testing of risk factor relationships much earlier in the disease process (Morris et al., 1999). Factors that are related to AD would also be expected to be related to cognitive decline, however, the reverse is not a given due to the other types of dementia that likely have different risk profiles. Also, dementia pathologies account for less than 50% of the variance in the decline in mental abilities with aging suggesting that there are causes of decline other than these well-characterized dementia diseases (Boyle et al., 2013). Included among these other causes of mental decline are B-vitamin deficiencies, hypothyroidism, and depression.

1.2 AD brain pathology

The neuropathological features of AD include the extracellular accumulation of amyloid-beta protein into neuritic plaques, hyperphosphorylation of tau-protein to form neurofibrillary tangles within neuron cells, neuron loss, synapse loss, and brain atrophy

(Schneider et al. 2009). One hypothesis is that oxidative stress and inflammation are the underlying causal mechanisms of AD pathology (Holmes 2013; Mecocci et al., 1994). The blood brain barrier (BBB) protects the brain from environmental insults that contribute to oxidative stress and inflammation. BBB dysfunction is an early pathological feature of AD and vascular dementia, and can be triggered by inflammatory stimuli (Takechi et al., 2012).

1.3 Lipids and the brain

Lipids are a class of molecules comprised of a number of subclasses, i.e., triglycerides (composed of fatty acids linked to a glycerol backbone), free fatty acids, sterols (cholesterol and cholesterol-related compounds), phospholipids, and other groups of compounds (Linscheer and Vergroesen, 1994). Lipids are the major source of brain dry weight because they are the basic structural component of neuronal cell membranes. Other important biological functions of lipid molecules include energy storage and molecular signaling (Linscheer and Vergroesen, 1994). Cholesterol may play an important role in AD (Puglielli et al., 2003). Specifically, cholesterol forms the core of the neuritic plaques that characterize AD, and it is thought that a primary role of the amyloid precursor protein (APP) is to clear excess cholesterol from the brain (Puglielli et al., 2003). The most established genetic risk factor for AD is the apolipoprotein E (APOE)- ϵ 4 allele, which has been associated with nearly a doubling in the risk of developing AD (Bennett et al., 2003; Evans et al., 1997). ApoE encodes one of several proteins involved in cholesterol transport between the gut, liver, and peripheral tissues and they are the predominant cholesterol transport proteins in the brain. A number of cohort studies that measured total blood cholesterol in mid-life found that participants with higher levels of total cholesterol or hypercholesterolemia had an increased risk of developing dementia in late-life compared with the participants who had normal or low cholesterol levels (Beydoun et al., 2010; Kivipelto et al., 2002; Mainous et al., 2005; Notkola et al. 1998; Reynolds et al., 2010; Solomon et al., 2007; Solomon et al., 2009; Whitmer et al., 2005).

1.4 Dietary lipids

Fatty acid composition is characterized by both the degree of unsaturation in the fatty acid chain and the configuration about the saturation. Fatty acid composition of the diet is one of the primary factors that affect blood cholesterol levels. Specifically, high ratio of unsaturated to saturated fatty acids results in a favorable blood cholesterol profile (Hunter, 1998). In contrast to the effects of fatty acids on blood cholesterol, dietary cholesterol has a limited effect and particularly in populations that consume a Western diet (Hunter, 1998; Keys et al., 1966; Mancini et al., 2004). Thus, this review is focused on non-cholesterol dietary lipids.

The major categories of dietary fatty acids are saturated, trans, monounsaturated and polyunsaturated fatty acids. The dietary fatty acids differ biochemically and are classified by the numbers of carbon atoms (length), the configuration of hydrogen atoms around the carbon-carbon double or triple bonds, and the position of unsaturation from the methyl end of the hydrocarbon chain (Linscheer et al., 1994). Food sources of fatty acids are products of both plant and animal origin. However, in humans, seeds and vegetable oils are the sole source of the two essential fatty acids, α -linoleic acid (18:2 n-6) and α -linolenic acid (18:3

n-3), which are polyunsaturated fatty acids. These fatty acids are considered essential because they are required for normal physiological function, cannot be synthesized within the body, and must be consumed to maintain good health. It is important to note that dietary fatty acids are also required for the adequate absorption of the lipid soluble vitamins E, A, D, and K and of the carotenoids. Many of these compounds function as antioxidants that may be linked to brain health.

Saturated fatty acids have no double bonds and are solid at room temperature (Linscheer et al., 1994). Most natural foods have varying compositions of fatty acids, however, meat and dairy products have a higher saturated fatty acid composition. Fruits and vegetables tend to be lower in total fatty acids and the composition is predominantly unsaturated. Trans fatty acids are made either by microbial metabolism in ruminants or manufactured through the hydrogenation of vegetable oil. In the hydrogenation process, hydrogen is added to monounsaturated and polyunsaturated fatty acid containing oils to make products such as margarine and shortening. The process allows for the solidification and enhanced stability of these oils to mimic the properties of butter and lard. Trans fatty acids improve the shelf life of food products and also can improve food texture and flavor. They are particularly hypercholesterolemic because they both increase LDL-cholesterol and decrease HDL-cholesterol (Mozaffarian et al., 2009).

Throughout the mid to late 1900's trans fatty acids were widely consumed in the United States (US), particularly from manufactured margarine products and baked goods. In the 1990's, scientific investigations linked trans fats to a higher risk of cardiovascular disease (Teegala et al., 2009), which prompted legislation in 2006 requiring the identification of the trans fatty acid content on food labels. As a result of vigorous public health messaging about the health risks of trans fats (i.e., partially hydrogenated vegetable oils) and manufacturer's reduction of trans fats in food products (most probably in response to the labeling mandate), trans fatty acid intake has decreased significantly in the U.S. from a mean of 4.6 g/d in 2003–2006 to 1.3 g/d in 2009 (Doell et al., 2012), which is a decrease of 72%. Trans fatty acid consumption also differs markedly by country and is historically low in the Netherlands and other European countries (Michels and Sacks, 1995). Thus, depending on a study's historical time period or country location, trans fatty acid intake may be at a low level for the entire study population.

This review is focused on the broadest classes of fatty acids (i.e., saturated, trans, monounsaturated and polyunsaturated) and does not describe the large body of literature on the specific types of n-3 and n-6 polyunsaturated fatty acids that have been reviewed previously (Barberger-Gateau et al., 2011; Cole et al., 2010; Morris, 2012).

2.0 Review of evidence

2.1 Animal and laboratory studies of dietary fats

Most of the animal and laboratory research on dietary fatty acids and the brain has occurred fairly recently and tends to support the findings of the epidemiological studies showing greater risk of dementia with high saturated and trans fatty acid intakes and lower risk with high unsaturated fatty acid intakes. Takechi and colleagues (2013) have shown that a high-

fat diet decreases the integrity of the BBB and results in cerebrovascular inflammation in amyloid transgenic mice fed either a high saturated fatty acid diet (20% of energy) or a high cholesterol diet. After 12 weeks on the diets, the BBB dysfunction of the mice on the high saturated fatty acid diet was increased 30-fold whereas dysfunction on the high-cholesterol diet was increased 7-fold. Mice who were also administered the lipid-lowering agent, probucol, while on these diets experienced no loss of BBB integrity or cerebrovascular inflammation, suggesting that higher blood cholesterol concentration is central to BBB dysfunction. In cell culture experiments, Grimm and colleagues (2012) found that trans fatty acids increased amyloidogenic APP and decreased non-amyloidogenic APP when compared to cis forms of oleic and polyunsaturated fatty acids. Further, the trans fatty acids in this study increased amyloid-beta ($A\beta$) aggregation. Yet another investigation of transgenic mice found that greater concentrations of $A\beta$ protein in the brain resulted from a Westernized diet of 40% saturated fatty acids over a 4-month period compared with a soy oil based diet (Oksman et al., 2006; Snigdha et al., 2012). conducted a study of aged dogs in which they demonstrated that a diet high in saturated fatty acids and low in monounsaturated fatty acids increased learning errors and decreased cognitive performance. Winocur and Greenwood (2005) found similar results in studies of transgenic mice spanning nearly two decades of research in which impaired learning and memory performance resulted from diets high in fat (40% of calories versus 4.5% in standard chow) and particularly diets high in saturated fatty acids. They concluded from their studies that a chronic high-fat diet impairs glucose regulation resulting in reduced glucose uptake in the hippocampus region of the brain.

In summary, chronic feeding of saturated and trans fatty acids at high levels to laboratory animals has been shown to result in BBB dysfunction, increased $A\beta$ aggregation, poorer cognitive performance, and reduced glucose utilization in the key brain regions.

2.2 Epidemiological studies of fats and cognitive decline

A number of prospective epidemiological studies have investigated the relationship of dietary fatty acid composition to the risk of developing dementia (Table 1). A major challenge in the interpretation of these studies is that most of them analyzed each type of fatty acid in models that were not adjusted for other types of fatty acids. Confounding is a likely explanation for the null results in these studies because all of the dietary fatty acids are moderately to highly positively correlated with one another. For example, in the Chicago Health and Aging Project (CHAP), dietary intake of monounsaturated fatty acid was highly correlated with dietary intakes of saturated fatty acids ($r=0.82$) and trans fatty acids ($r=0.70$), but saturated and trans fatty acids were associated with an *increased* risk of AD and monounsaturated fatty acid was associated with a *decreased* risk of AD (Morris et al., 2003). Failure to adjust for other types of fatty acids in the model resulted in negative confounding in that the estimates of effect were smaller than the “true effect” or closer to the null. The analyses of monounsaturated fatty acid intake in the CHAP study indicated substantial negative confounding; the estimated odds ratio of incident AD for persons in the top quintile compared with the first quintile was $OR=0.8$ without adjustment for intakes of other fatty acids and $OR=0.2$ with adjustment (Morris et al., 2003). Similarly, for the analyses of trans fatty acids in the model without other fatty acids included, the odds ratios for intake

quintiles 2 to 5 ranged from 1.8 to 2.9 and these increased to 3.4 to 5.2 after the adjustment for other fatty acids.

The inclusion of all of the highly correlated fatty acids in the analytic model can be statistically problematic because of multicollinearity among the fatty acid variables, which can inflate the standard errors of the estimates and thus lead to a failure to reject a false null hypothesis. The magnitude of this problem is greater for studies with small sample size. In the CHAP study, saturated fatty acid intake in the fifth quintile was associated with double the risk of incident AD compared to the first quintile of intake (OR=2.2; 95% confidence interval: 1.1–4.7) (Morris et al., 2003). With adjustment for other types of fatty acids, the odds ratio increased to 3.6 (indicating confounding by other fats) and the 95% confidence interval increased substantially (0.7–18.6) including the null value of 1.0 (indicating inflated standard error attributable to multicollinearity). The same problem of multicollinearity and inflated standard errors with fatty acid adjustment was evident for the other fats; the 95% confidence interval (1.5–18.5) for the fifth quintile of trans fatty acid intake widened but was still statistically significant, whereas the 95% confidence interval for monounsaturated fatty acids was also very wide (0.2 – 1.5) and included the null value. Dietary intake of n-6 polyunsaturated fatty acids was linearly associated with a lower AD risk (Q5 versus Q1 OR=0.3, p-value for linear trend=0.02) in the model without fat adjustment, but when other fatty acids were included the linear trend became non-significant (p=0.10). The non-significant OR in the adjusted model is likely a result of the inflated standard error due to multicollinearity given that the quintile effect estimates did not change with and without the adjustment.

The only other incident dementia study, the Cardiovascular Risk Factors, Aging and Dementia (CAIDE) study that adjusted for all types of fatty acids in the analyses (Laitinen et al., 2006) had somewhat similar findings to the CHAP study. In this study, only the second quartiles of unsaturated fat and of saturated fatty acids versus the first quartiles of intake had a statistically significant relationship to late-life dementia. The authors interpreted this finding as evidence of non-linear relationships of these fatty acids with dementia. However an alternative explanation is that the fat intake assessment in this study likely had considerable measurement error due to the incomplete measurement of fat intake. In this study, the respondents were only queried about their use of diet spreads and milk products, thus many other sources of fat in the diet were not included in the assessment of fat intake. Another important source of measurement error was the single dietary assessment over 21 years of follow-up (Laitinen et al. 2006). It is difficult to interpret the findings of the other studies of fatty acid intake and dementia (Table 1) because other types of fatty acids were not accounted for in the analyses.

Another method of analyzing fat composition is to model the ratio of unsaturated to saturated fatty acid intake. In the CHAP study, persons in the highest quintile of polyunsaturated to saturated fatty acid intake (P/S median = 0.9) had a statistically significant 70% reduction in the risk of developing AD over 3.9 years. To the best of our knowledge, no other study of incident dementia has investigated the relation of P/S ratio to dementia risk.

2.3 Epidemiological studies of dietary fats and cognitive decline

The majority of studies that examined the relationship of dietary fat composition to a decline in cognitive abilities adjusted for other types of fatty acids in the analyses (Beydoun et al., 2007; Devore et al., 2009; Eskelinen et al., 2008; Heude et al., 2003; Morris et al., 2004; Okereke et al., 2012) or at least partially adjusted for other fatty acids (Naqvi et al., 2011; Vercambre et al., 2010). Those studies that adjusted for other fatty acids consistently showed increased rates of cognitive decline with higher intakes of saturated fatty acids. Further, in all but one of these studies, decreased rates of cognitive decline were observed with higher intakes of either monounsaturated fatty acids (Okereke et al., 2012; Devore et al., 2009; Morris et al., 2004; Vercambre et al., 2010; Naqvi et al., 2011; Solfrizzi et al., 2006) or polyunsaturated fatty acids (Beydoun et al. 2007; Eskelinen et al., 2008; Morris et al., 2004; Roberts et al., 2012; Solfrizzi et al., 2006; Vercambre et al., 2010), although many of the associations were marginally statistically significant (indicated by gray arrows in Table 2) (Devore et al., 2009; Eskelinen et al., 2008; Morris et al., 2004; Roberts et al., 2012; Solfrizzi et al., 2006; Vercambre et al., 2010). Only two of the five studies (Devore et al., 2009; Eskelinen et al., 2008; Morris et al., 2004; Vercambre et al., 2010; Solfrizzi et al., 2006) that examined the relationship of the ratio of unsaturated to saturated fatty acids (Devore et al., 2009; Morris, et al., 2004) to cognitive decline observed a decrease in the rate of decline. Among the studies that adjusted for other types of fatty acids, trans fatty acid intake was associated with a greater rate of decline in the CHAP study (Morris et al., 2004) and among diabetics in the Nurses' Health Study (Devore et al., 2009), however there was no association in the Women's Health Study (WHS) (Okereke et al., 2012). One potential explanation for the null finding for trans fatty acids in the WHS is that the intake levels were below the threshold to affect the brain. Compared with the trans fatty acid intake levels in the CHAP and NHS, reported levels for the WHS were very low at a median 1.8% of energy for the highest quintile of intake.

3.0 Discussion

This review outlined several lines of evidence that support a relationship between dietary fatty acid composition and the risk of developing dementia. First, the composition of fatty acids in the diet is one of the more important determinants of the blood cholesterol profile, and cholesterol plays a central role in AD pathology. Further, the most important genetic risk factor for AD, APOE- ϵ 4, is involved in cholesterol transport, and the evidence from studies of mid-life blood cholesterol support a relationship of increased risk of late-life dementia among individuals with a hypercholesterolemic lipid profile during mid-life. There is accumulating evidence from animal models suggesting a number of biological mechanisms underlying an effect of dietary fats on dementia. Even though the epidemiologic literature appears mixed for demonstrating the associations between dietary fatty acid consumption and the risk of developing AD or dementia, only the CHAP study took into account the confounding from different types of fatty acids, which is considerable and likely contributed to the null findings in many of the dementia studies. The CHAP study found an increased risk of AD with higher consumption of saturated and trans fatty acids and decreased risk with higher consumption of monounsaturated and polyunsaturated fatty acids. A similar pattern emerges from the review of the studies that investigated the

relationship of dietary fatty acid composition to cognitive decline. However, many more of these studies adjusted statistically for other fatty acids. Of all the different types of fatty acids, the findings are most consistent for an increased risk of cognitive decline with a higher intake of saturated fatty acids.

Future studies of fatty acid composition and dementia can best inform the field by analyzing data adjusting for the different types of fatty acids. Further, primary analyses of these data should be presented without statistical adjustment of cardiovascular conditions given the established effects of dietary fatty acid composition on these conditions. Statistical control for these intermediary factors would result in the underestimation of the effects of dietary fatty acids on dementia. Also, interpretation of findings across studies would be optimized by presentation of the analyses with fatty acids modeled in quintiles along with the range of intake for the quintiles in both grams per day and percent energy. This would allow for determination of the levels of intake at which a particular fatty acid results in a benefit or risk of dementia. Much more research is required to understand whether and to what extent dietary fatty acid composition is related to the development of dementia and the biological mechanisms that underlie these relationships.

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Table 1

Prospective Studies of Dietary Fats and Dementia

Study*	N	Follow-Up	Exposure	Outcome	Fats Adjusted	Saturated	Trans	MUFA**	PUFA**	U/S**
Ronnenan, et al., 2012, ULSAM	838	35 y	Serum	AD	---	↓	--	--	↑	
Samieri, et al., 2008, 3-City	1,214	4 y	Plasma	Dementia	---		--	--	--	
Laitinen, et al., 2006, CAIDE	1,449	21 y	Diet (spreads)	AD	Yes	↑	↑	↑	↑	
Morris, et al., 2003, CHAP	815	3.9 y	Diet	AD	Yes	↑	↑	↑	↑	↓
Engelhart, et al., 2002, Rotterdam	5,395	6 y	Diet	AD	No	↓	↓	--	--	
Luchsinger et al., 2002, WHICAP	980	4 y	Diet	AD	No	↑	↑	--	--	
Kalmijn, et al., 1997, Rotterdam	5,395	2 y	Diet	AD	No	--	--	--	--	
				Vascular Dementia		↑			--	

* ULSAM=Uppsala Longitudinal Study of Adult Men; CAIDE= Cardiovascular risk factors, Aging and Incidence of Dementia; CHAP=Chicago Health and Aging Project; WHICAP=Washington Heights-Inwood Columbia Aging Project;

** MUFA=Monounsaturated fatty acids ; PUFA=Polyunsaturated fatty acids; U/S = Unsaturated to saturated fat ratio

↑ = Statistically significant increased risk (downward arrow=decreased risk)

↑ =Marginally statistically significant increased risk (downward arrow=decreased risk)

Table 2

Prospective Studies of Dietary Fats and Cognitive Decline

Study*	N	Follow-Up	Exposure	Outcome	Fats Adjusted	Saturated	Trans	MUFA**	PUFA**	U/S**
Okereke, et al., 2012, WHS	6,183	9 y	Diet	Global Cognitive	Yes	↑	--	↑	--	--
Roberts, et al., 2012, Mayo	937	3.7 y	Diet	MCI	No	--	--	--	↑	↑
Naqvi, et al., 2011, WHI	482	3 y	Diet	Global Cognitive	Partial	--	--	↑	--	--
Vercambre, et al., 2010, WACS	2,551	8.9 y	Diet	Global Cognitive	Partial	--	↑	↑	↑	--
Devore, et al., 2009, NHS	1,486	1.8 y	Diet	Global Cognitive	Yes	↑	↑	↑	--	↑
Eskelinen, et al., 2008, CAIDE	1,449	21 y	Diet	MCI	Yes	↑	--	--	↑	--
				Global Cognitive		↑	--	--	--	--
Beydoun, et al., 2007, ARIC	2,251	6 y	Plasma	Global Cognitive	Yes	↑	--	--	↑	↑
Morris, et al., 2006, CHAP	2,560	6 y	Diet	Global Cognitive	Yes	↑	↑	↑	↑	↑
Solfrizzi et al., 2006, ULSAM	704	8.5 y	Diet	MMSE	No	--	--	↑	↑	--
Heude, et al., 2003, EVA	246	4.4 y	Erythrocytes	MMSE	--	↑	--	--	↑	↑

* WHS=Women's Health Study; Mayo=Mayo Clinic; WHI=Women's Health Initiative; WACS=Women's Antioxidant Cardiovascular Study; NHS=Nurses' Health Study; CAIDE= Cardiovascular risk factors, Aging and Incidence of Dementia; ARIC=Atherosclerosis Risk in Community Studies; CHAP=Chicago Health and Aging Project; ULSA=Uppsala Longitudinal Study of Adult Men; EVA= Etude du Vieillessement Artériel

** MUFA=Monounsaturated fatty acids ; PUFA=Polyunsaturated fatty acids; U/S = Unsaturated to saturated fat ratio

↑ = statistically significant greater rate of cognitive decline (downward arrow=slower rate of cognitive decline)

↓ = marginally statistically significant slower rate of cognitive decline