GSC Advanced Research and Reviews

eISSN: 2582-4597 CODEN (USA): GARRC2

Cross Ref DOI: 10.30574/gscarr

Journal homepage: https://gsconlinepress.com/journals/gscarr/

(REVIEW ARTICLE)

Check for updates

Reducing excess dietary saturated fat intake to improve cognition in vascular dementia

Steve Michael Blake *, Thomas Harding, Catherine Peterson Blake and Patricia Lynn Borman

Maui Memory Clinic and Department of Geriatrics, University of Hawaii, HI, USA.

GSC Advanced Research and Reviews, 2022, 12(02), 122–135

Publication history: Received on 16 July 2022; revised on 17 August 2022; accepted on 21 August 2022

Article DOI: https://doi.org/10.30574/gscarr.2022.12.2.0220

Abstract

Reducing excess dietary saturated fatty acids (SFAs) may be a therapy to slow cognitive decline in vascular dementia (VaD). It has been well established that lower levels of dietary SFAs reduce risk of cognitive decline and vascular dementia. In patients who consume high amounts of SFAs, limiting intake of SFAs could improve cognition. Some trials have seen a reduction in atherosclerotic lesions and memory problems with diets reduced in total and saturated fat. It has also been well established that excess dietary SFAs increase serum cholesterol and risk of atherosclerosis, so reducing dietary SFAs could reduce arterial clogging, potentially improving perfusion and cognition. Many studies show that those with lower dietary SFAs have decreased blood-brain barrier damage and neuroinflammation, so reducing excess dietary SFAs could reduce neuroinflammation. Excess dietary SFAs impair neurovascular coupling, potentially leading to brain pathologies ranging from subtle cognitive deficits to severe dementia. Studies on stroke survivors show that limiting the consumption of SFAs improves cognitive functions after stroke. We will show that reducing excess dietary SFAs can produce protective effects on cognitive functioning. More studies are needed to determine if reducing excess dietary SFAs can improve memory and other cognitive functioning in those with vascular dementia.

Keywords: Vascular dementia; Saturated fat; Atherosclerosis; Memory; Cognition; Neurovascular coupling

1. Introduction

Vascular dementia (VaD) is an impairment of memory and other cognitive functioning due to a reduction in cerebral blood flow, which can limit glucose and oxygen supply to the brain.[1] Some estimates show that, worldwide, cerebrovascular disease is the most common contributor to cognitive impairment. [2] Vascular dementia is the second most common form of dementia after Alzheimer's disease (AD), and mixed dementia (with both AD and VaD) is common. [3] The recently described term "vascular cognitive impairment" encompasses all cardiovascular factors that lead to dementia syndromes, including impaired brain perfusion. [4]

Drugs currently used in the treatment of cognitive impairment and dementia have a limited therapeutic value. The drugs donepezil or memantine are used, but brain neurodegeneration continues. A recent safety study shows that donepezil has "minimal effects on cognition" with risk of vomiting increased 76% and risk of diarrhea increased 62%, compared to placebo.[5] Memantine may have small positive effects, but possible severe side effects, including blood clots, psychosis, and heart failure. Aducanumab may not be effective, and has possible side effects of brain swelling and bleeding. Reducing VaD through a reduction in excess dietary SFAs is safe and side effects include lowered risk of both ischemic heart disease and stroke. [6]

*Corresponding author: Steve Michael Blake, Email: steve@drsteveblake.com
Maui Memory Clinic and Department of Geriatrics, University of Hawaii, HI, USA.

Vascular dementia can result from ischemic reduction of blood flow to neurons, often from many small strokes. Chronic insufficiency of cerebral blood supply can also contribute to VaD. Cerebral hypoperfusion has been shown to cause attention and memory deficits as well as cognitive dysfunction. [7] Cerebrovascular dysfunction is also a major contributor to VaD.

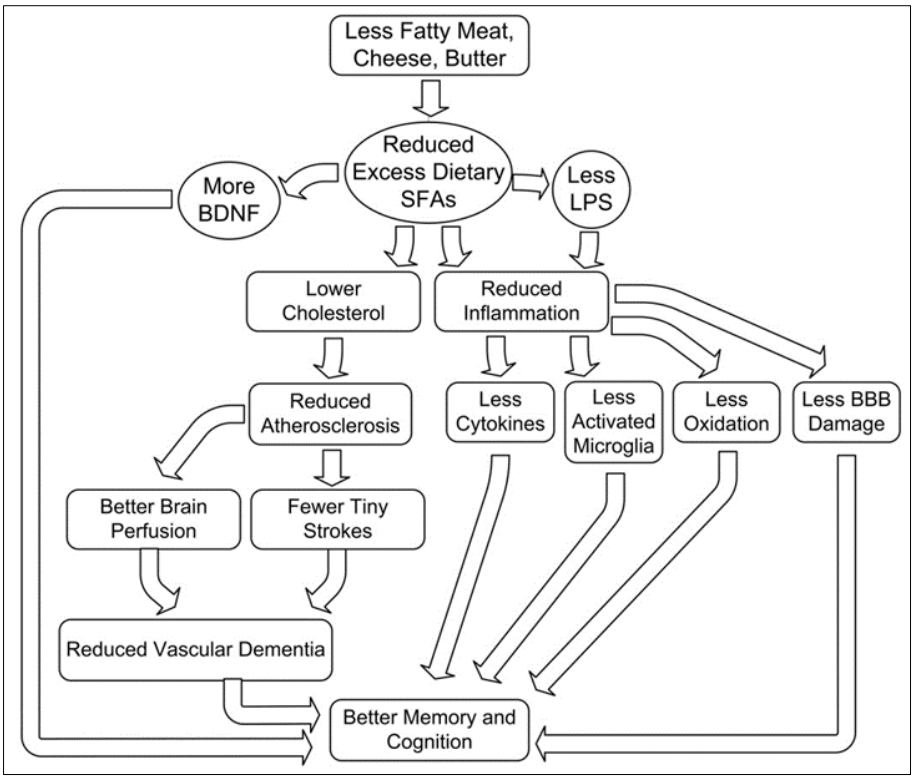

Figure 1 How reducing SFAs improves cognition. SFA=saturated fatty acids, BDNF=brain-derived neurotrophic factor, LPS=lipopolysaccharides, BBB=blood-brain barrier

Vascular dementia can be a result of a major stroke. VaD can result from subcortical ischemia, including small-vessel occlusion. Contributors to VaD are multi-infarcts, including in medium-to-large blood vessels. VaD can contribute to Alzheimer's pathologies and may be present in many dementia cases.[8] The accumulation of small, even miniscule ischemic lesions has been emphasized in recent years as an important contributor to cognitive impairment and dementia. Microbleeds may also be a contributing factor.

Both retrospective and prospective studies show that consumption of diets low in SFAs decrease risk for development of dementia.[9] The major sources of SFAs in the United States include fatty meats, cheese, milk, margarine, and butter.[10] In recent years, coconut oil and products containing coconut oil have become additional dietary sources of SFAs.

The major proposed biological mechanisms for the negative cognitive effects of diets high in SFAs include: atherosclerosis (AS), reduced brain perfusion, oxidative stress, neuroinflammation, and disruption of the cerebrovascular epithelial cells. In addition, insulin resistance increased by excess dietary SFAs may reduce glucose availability to neurons. [11] A diet high in fat/SFAs may contribute to decreased glucose uptake by the brain, leading to insufficient energy supply and decreased neuronal functionality. [12] Atherosclerotic and cardioembolic diseases combined appear the most common subtypes of vascular brain injury. Atherosclerosis is one of the best predictors of vascular cognitive impairment. [13]

Lower dietary SFAs have been shown to decrease oxidative damage to neurons, decrease neuroinflammation, and maintain the integrity of the blood-brain barrier (BBB). [14, 15] Excess dietary SFAs can damage the BBB, increasing risk of AD and VaD. [16] Neurovascular dysfunction from excess dietary SFAs can occur before the onset of VaD and can eventually lead to dysregulation of cerebral blood flow and BBB damage. [17]

Cerebrovascular endothelial cell (CEC) dysfunction, following increased neuroinflammation from excess SFAs, can occur during the onset of VaD and can eventually lead to dysregulation of cerebral blood flow and BBB damage. This can be

followed by the activation of microglia and an inflammatory environment in the brain. CECs are core components of the BBB. White matter, neuronal axons, and synapses are compromised in this SFA-triggered neuroinflammatory process, leading to cognitive impairment. CEC dysfunction not only contributes to BBB compromise, exposing neuronal cells to harmful substances, but also affects neurovascular coupling, so that cerebral blood flow (CBF) cannot respond in a timely manner to neuronal activity. [18]

2. Reducing excess dietary SFAs can improve vascular dementia

Higher dietary intake of SFAs increased long-term poor cognitive outcomes in stroke patients, while lower intake of SFAs improved cognitive outcomes. Lower dietary SFAs have been found to improve cognition in neuropsychological testing. One mechanism is that a diet rich in SFAs can disrupt the BBB to impair cognition. The dietary factor that improved VaD to positively influence cognitive functions in a group of stroke survivors was limiting the excess consumption of SFAs by reducing whole-fat dairy products and red meat. [19] These changes in dietary habits have improved survival from stroke, and may also improve vascular dementia. [20] Consumption of diets high in plants and lower in SFAs was correlated with greater insulin sensitivity and a lower risk of age-related cognitive decline. [21]

A group of subjects with amnestic mild cognitive impairment (MCI) were fed either a diet high in SFAs (>25% of calories) or low in SFAs (<7%). Delayed visual memory improved after completion of 4 weeks of the low SFAs diet. In addition to better visual memory test scores, the low SFAs group also had improved CSF markers of cognitive impairment. [22] In another 4-week study, delayed visual memory scores improved after a diet low in SFAs and sugar, but worsened with a diet high in SFAs and sugar. [23] The American Heart Association maximum of 5-6% of calories as saturated fat (about 12 g/day) to reduce cardiovascular risk could be used as a guideline to reduce VaD risk and progression. [24] A group of students who consumed a low fat/sugar diet had improvement in hippocampal sensitive memory tasks, compared to a group who ate a high fat/sugar diet. The authors concluded that Western diets high in SFAs may disrupt hippocampal function. [25] A recent meta-analysis showed that diets high in SFAs adversely impact human hippocampal volume and functioning. Lower intake of SFAs was associated with less impairment in hippocampal-dependent relational memory, improvement on a visuo-spatial learning task, and improvement on a verbal recognition memory task. [26]

Dietary intervention may play a key role in the treatment of cognitive decline in aging. Lower dietary intake of SFAs is associated with better cognition and a lower risk of vascular dementia. Diets lower in SFAs were associated with improved memory. Improving the dietary profile to reduce intake of SFAs may produce protective effects on cognitive functioning. [27]

There is an abundance of evidence in animals and humans that even a single meal with high SFAs can worsen cognition. Conversely, there is evidence that adults who ingest a diet lower in SFAs show improvements in brain chemistry and cognitive profiles. Further evidence shows that reducing dietary SFAs, even for a relatively short duration, in older adults can improve cognition, indicating that reducing SFAs in this age group is a viable treatment option. [28]

Elders with the lowest intake of SFAs had the best performance on the Mini-Mental State Examination and Pfeiffer's Mental Status Questionnaire. [29] Reducing high dietary SFAs in mice led to a complete amelioration of memory loss, which was partly associated with rescue of cerebral blood flow. [30]

Episodic memory, together with spatial and contextual associative memory, is compromised after only one day of a high SFA diet in mice. These memory deficits are rapidly reversed by switching mice from a high-fat diet back to a low-fat diet. These data also support dietary advice that reducing saturated fat consumption is a viable approach to healthier brain aging. [31]

Clinical studies show that the reduction of hypertriglyceridemia improved cerebral blood flow and function on the cognitive capacity screening examination. [32, 33] Higher SFAs in plasma reduced cognitive function in Chinese adults, as measured by the Mini Mental Status Examination and the Montreal Cognitive Assessment, indicating that reducing SFAs may improve cognition. [34]

3. Lower dietary SFAs contribute to improved cognition and reduced vascular dementia

Excess SFAs decrease cognitive performance. [35] Reducing dietary SFAs has been linked to a reduced risk of dementia. Vascular dementia risk was three times less with lower intakes of SFAs. [36] A diet high in SFAs reduced attention and cognitive function in adults in only 7 days. [37] Another study found that a diet high in SFAs impaired attention, processing speed, and mood after only 5 days in men averaging 22 years of age. [38] In the Women's Health Study, lower intake of

SFAs was associated with better global cognition and verbal memory in 6183 women. [39] Risk of verbal memory decline was increased 65 percent with higher SFAs in 4 years. [40] Several human-based studies showed that lower intake of dietary SFAs was associated with a reduced incidence of MCIand a reduced risk of dementia later in life. [41] A high intake of SFAs has been associated with impairments in verbal and prospective memory in adults. [42] A large meta-study found that a lower intake of dietary SFAs was significantly associated with half the risk of dementia (relative risk 2.05). [43]

Dyslipidemia from a high-fat diet can contribute to the development of atherosclerotic plaque, leading to microvascular dysfunction, associated with worse cognitive performance. [44] Higher intake of SFAs was associated with a 15% to 19% increased risk of impairment in memory, psychomotor speed, and cognitive flexibility. [45] Accuracy on both the relational and item tests was better with a low intake of SFAs in children. [46]

Detrimental effects of a high SFA diet include loss of blood supply to the brain, which can contribute to the loss of white matter and have an adverse effect on executive functioning and processing speed.[47] In middle-aged adults, high consumption of SFAs is associated with poorer memory and may contribute to a reduction in total hippocampal volume. [48] Blood-brain barrier damage increased 30 times in 12 weeks with excess dietary SFAs, raising risk of neuroinflammation and dementia. [49] Higher intakes of SFAs increased cognitive decline in some studies with a relative risk of 2.6, 3.6, and 2.74 compared to lower SFAs intakes. [50] Excess intake of SFAs is correlated with impaired cognitive function. [51]

A high-fat/high-cholesterol diet had detrimental effects on hippocampal dendritic integrity and increased the activation of microglial cells in the hippocampus. [52] This may be partially due to micro-vascular pathology in the cerebral cortex and vascular degeneration. [53] There was found to be a reduced risk of cognitive decline among persons whose diets were low in SFAs and trans-fatty acids (TFAs). [54]

Data have established that high fat, low carbohydrate ketogenic diets can disrupt cognition and trigger glial activation.[55] Low dietary intake of SFAs reduced the risk of: cognitive decline, poorer global cognitive function and prospective memory, dementia, and AD. Abundant intake of SFAs from milk products at midlife was associated with poorer global cognitive function, poorer prospective memory, and with an increased risk of MCI (odds ratio 2.36), after adjusting for demographic factors, vascular factors, other fats, and ApoE (Apolipoprotein E). [56]

3.1. Reduced brain-derived neurotrophic factor

A 30 percent sat fat breakfast (versus 6%) in 100 students reduced hippocampal memory 16 percent in just four days. [57] Even in 3 days, high saturated fat diets reduce hippocampus-dependent learning and memory. Mechanisms include reduction of: synaptic plasticity, acetylcholine, dopamine, serotonin, and brain-derived neurotrophic factor (BDNF). [58] Diets high in SFAs reduce BDNF, resulting in reduced synaptic plasticity and reduced neurogenesis in the hippocampus.[59] High dietary intake of SFAs can reduce the formation of new neurons by inhibiting the formation of BDNF in children. [60] Excess SFAs can impair hippocampal neurogenesis and neural progenitor cell proliferation through increased lipid peroxidation (malondialdehyde) and decreased BDNF. [61] In one study, high levels of the antioxidant vitamin E reduced the damage to cognition and reversed the lowering of BDNF that resulted from a diet high in SFAs, thus showing the involvement of oxidation. [62] A diet high in SFAs reduced the ability to learn in the hippocampus by limiting BDNF and neurotransmitter release, thus impairing memory.[63] In experimental studies, SFAs have decreased the levels of hippocampal BDNF that are needed for neuronal plasticity and the maintenance of cognitive functions. [64]

3.2. Mild cognitive impairment

An increasing body of epidemiological evidence suggests that elevated SFAs could have negative effects on age-related cognitive decline and MCI. [65] An Australian study found that diets high in SFAs were linked with a decline in short-term and long-term memory recall, reduced memory speed, and reduced cognitive performance. [66] Prevalence of MCI more than doubled (relative risk=2.20) in the highest quartile of intake of SFAs compared with the lowest in a large Chinese trial. [67] In addition to adult studies, prepubescent children who consumed more SFAs showed impairments in hippocampal-dependent relational memory and cortical-dependent item memory relative to children who consumed less SFAs. [68]

4. Excess dietary SFAs increase neuroinflammation and damage memory

High levels of SFAs killed off over 50% of brain cells via excess inflammation and microglial activation in microglial cell cultures. Palmitic acid was found to be the most inflammatory of the SFAs. [69] Meat, chicken, coconut oil, and dairy products contain large amounts of palmitic acid. A cross-over trial showed improved brain functioning and much lower levels of the inflammatory cytokines tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6) in just 2 weeks when

changing from palmitic acid to oleic acid.[70] Diets high in SFAs increase brain inflammation resulting in microglia activation and inflammatory cytokine release. SFAs can cross the blood-brain barrier and directly activate microglial toll-like receptors. [71] Toll-like receptors can then activate nuclear factor kappa-B (NF-kB), initiating a cascade of inflammatory cytokines, killing brain cells.

Diets high in SFAs compromise the hippocampus by sensitizing immune cells by activating microglia, thus priming inflammatory responses to subsequent challenging stimuli. Diets high in SFAs have been linked to elevated pro-inflammatory cytokines, which, in the hippocampus, can lead to deterioration of many mechanisms that enable synaptic plasticity and, in turn, long-term memory. [72] A diet chronically high in SFAs can lead to increased microglial activation, increased hippocampal amyloid burden, and reduced memory performance. [73] Microglia are important immune cells in the brain, accounting for approximately 16% of the total number of central nervous system (CNS) cells. However, when microglia are activated, this reduces synaptic plasticity and directly leads to cognitive impairment. [74]

Excess intake of dietary SFAs, TFAs, and cholesterol led to alterations in hippocampal morphology and inflammatory activation, marked by increased activation of microglial cells, with SFAs having the greatest effect. [75] Foods high in SFAs increase absorption of inflammatory lipopolysaccharides into the bloodstream. Bacteria are killed during the cooking of meat, chicken, fish, and dairy products. The cell membranes of gram-negative bacteria (lipopolysaccharides, or endotoxin) trigger immune system inflammation through the toll-like receptors. [76]

Diets high in SFAs and cholesterol reduce BBB integrity and can activate microglia. [77] Inflammatory and innate immune responses can be activated by increased levels of serum lipids, such as cholesterol and saturated long-chain fatty acids. The saturated free fatty acids palmitic acid and lauric acid have both been shown to trigger inflammatory signaling. [78]

4.1. SFAs increase inflammatory cytokines

Excess dietary SFAs increase inflammation and free radical damage. [79] Microglia likely act as neuroinflammatory intermediaries between overload of SFAs and neurodegeneration. Lipid-laden microglia trigger oxidative stress and release proinflammatory cytokines. [80] Examples of pro-inflammatory cytokines that have been shown to cross the BBB include interleukin-1 (IL-1), IL-6, and TNF-α. Pro-inflammatory cytokines can also be produced by cells within the brain parenchyma, specifically by microglial cells, astrocytes, and cerebrovascular endothelial cells of the BBB. IL-1 and IL-6 receptors are located all over the brain, but they are particularly numerous in the hippocampus, a vital area of learning and memory. Proinflammatory cytokines, increased by SFAs, have been shown to have direct detrimental effects on hippocampal circuitry and cognition. [81]

5. Lowering serum cholesterol by reducing dietary SFAs decreases risk of vascular dementia

Diet-induced high cholesterol is one of the key factors that increases neuroinflammation and impairs cognition. [82] Midlife serum cholesterol predicts old age mixed dementia (including AD and VaD). Higher serum cholesterol at midlife predicted a 67% increase in risk of vascular and mixed dementia. Mixed dementia was estimated to constitute 57% of all dementia cases in Sweden. [83] Lower dietary cholesterol was associated with a reduced risk of impaired memory and cognitive function. [84]

Diets rich in red meat, poultry, and dairy products can have excess amounts of SFAs, mainly myristic, palmitic, and stearic acids, which are linked to higher cholesterol synthesis in the liver. By increasing low-density lipoprotein (LDL) cholesterol, SFAs promote AS and vascular aspects of dementia. Those with diets lower in SFAs and TFAs showed reduced cognitive decline compared with those with higher SFAs/TFAs diets. SFAs and TFAs increase LDL levels, leading to accelerated AS, and so promoting the onset of VaD. [85]

Fatty acids impact cognition in several ways. Consumption of excess SFAs can accelerate AS, promote thrombogenesis, and impair fibrinolysis to increase blood clots. [86] This promotes the progression of VaD because reduced blood flow and microinfarctions can cause long-lasting hypoxia in the brain. [87]

Reduced dietary SFAs are associated with reduced cholesterolemia. Hypercholesterolemia and hypertension promote intracranial atherosclerotic disease and carotid artery stenosis, which disrupt cerebral blood flow and trigger ischemic strokes and vascular dementia. [88] High consumption of SFAs and total fats promote hypercholesterolemia, risk of cardiovascular disease, and impaired intellectual function, suggesting that reducing levels of SFAs may improve cognitive performance in humans. [89] High serum cholesterol levels, via high dietary intake of SFAs in midlife, increase the risk of dementia in later life. Conversely, a diet low in SFAs, like the Mediterranean diet, is inversely related to dementia risk. [90]

Atherosclerotic plaques contained 20 times more cholesterol, and 45 times more oxysterols (oxidized cholesterol), than a healthy endothelium. Oxysterols increase arterial plaque and can make arterial plaque prone to rupture, potentially increasing vascular dementia. Oxysterols can cross the BBB, increasing inflammation in the brain. [91] High dietary cholesterol intake was significantly associated with accelerated cognitive decline and an increased risk of impaired memory. [92]

6. Reducing excess dietary SFAs can reduce risk of atherosclerosis and vascular dementia

A high-fat diet accelerates progression of AS, thus increasing VaD disease severity. Individuals can develop hypercholesterolemia and dementia with elevated LDL levels through excess dietary intake of SFAs. [93] Vascular dementia is strongly associated with cerebral AS, which can increase local inflammation caused by the accumulation of cholesterol, other lipids, and lipid-laden foamy macrophages. Atherosclerosis is characterized by the accumulation of oxidized LDL and cholesterol in the endothelium. The LDLs are engulfed by phagocytes to form foam cells, increasing inflammation. The narrowing of the lumen caused by gradually expanding atheromatous plaque restricts blood flow, reducing perfusion. Atherosclerotic plaque is a biomarker of AS, shown to also be one of the independent predictors of VaD in the elderly. [94] Activated glia and pericytes respond and contribute to intracranial AS and ischemia. [95] In one study, more than 77% of postmortem AD brains had circle of Willis AS, compared to 47% in controls. [96] AS can be reversible, thus reducing VaD. Atherosclerotic clogging was reduced to one third using a diet made up of 65 percent fruits, vegetables, and whole grains, coupled with exercise over 7 years. This diet reduced AS plaque and improved flow-mediated dilatation. [97]

Patients with less AS had fewer memory problems. Tiny strokes can add up to VaD. Patients with fewer clogged carotid arteries showed better performance in language, navigational abilities, and attention. [98] Researchers followed those with carotid artery atherosclerotic clogging for 3 years. Patients with the fewest clogged carotid arteries were 4 to 15 times less likely to have cognitive deterioration. [99] Clearing carotid arteries with a stent improved memory 7%. [100]

Converging evidence suggests that AS may play a direct role in the progression of VaD through stenosis, occlusion, and intima-media thickening, which are all characteristics of AS. Impaired blood flow and cerebral atrophy are characteristics of VaD that are related to these AS changes. Chronic hypoperfusion from stenosis can increase neuroinflammation by activating microglia cells, eventually resulting in white matter lesions and neurodegeneration, leading to cognitive impairment and, ultimately, to VaD. [101]

6.1. Atherosclerosis reduces brain blood supply

Atherosclerosis affecting VaD can be divided into several categories: cerebral atherosclerosis that affects distal microscopic vessels, intracranial atherosclerotic disease that affects cerebral arteries, and large-vessel disease affecting carotid arteries supplying the brain. [102] Hypoperfusion can lead to low glucose levels, endothelial dysfunction, and a decrease of nitric oxide bioavailability. This restricted brain circulation can also increase vascular damage and the excess production of damaging mitochondrial reactive oxygen species. [103]

Atherosclerosis can increase vessel stenosis and occlusion, thereby reducing cerebral blood flow. Excess dietary SFAs can elevate serum cholesterol, promoting a cascade of cerebrovascular cholesterol deposition, inflammation, ischemia, neuronal injury, and cognitive impairment. [104] Chronic brain hypoperfusion from blood vessel thickening and dysfunction contributes to memory loss. Often characterized by cerebral infarcts, vascular damage is a critical cause of neuronal loss and synaptic disintegration leading to cognitive dysfunction. [105] A clinical trial showed that high consumption of SFAs may prompt deleterious changes in vascular function and reduce brain blood perfusion. [106]

Even transient ischemia can lead to hypoxia and hypoglycemia, stimulating neuronal excitotoxicity, and stimulating astrocyte activation. Excitotoxicity and astrocyte activation can lead to glutamate activation and neuronal death through mitochondrial autophagy. [107]

6.2. Mid-life atherosclerosis correlates with VaD

AS plays an important role in the development of VaD, and can predict VaD risk. Mid-life AS increased the risk of VaD 20 years later. More carotid plaque in mid-life correlated with a 90% increased risk of VD later in life. [108] People with elevated blood cholesterol at mid-life were 2-3 times as likely to have cognitive impairment, and this risk increased with higher cholesterol levels. [109] Vegetarians with a lower risk of AS also had a lower incidence of cognitive impairment. Midlife vascular disease plays a crucial part in the subsequent development of dementia. [110]

6.3. Markers of Atherosclerosis that also indicate VaD

Intima media thickness (IMT) is an important AS biomarker that can be measured by ultrasonography. Higher midlife IMT has both a close association with VaD and a strong relationship with increased risk of dementia in general. Higher IMT increased risk of VaD 32% and small vessel disease 47%. [111]

Flow-mediated dilatation (FMD) measures endothelial vasodilatation. It is one of the most sensitive predictors of vascular function in both AS and cognitive decline. Low FMD has been correlated with VaD. Patients with VaD display endothelial dysfunction, also found in AS. [112]

Ankle-brachial index (ABI) is a quick and inexpensive measurement and is a biomarker of AS. Low ankle-brachial index is associated with reduced cognition and a higher susceptibility for cognitive impairment. [113]

7. Excess dietary SFAs can increase neurovascular damage, increasing cognitive impairment

Studies that utilize high-fat diets, containing high levels of SFAs, implicate impaired neurovascular function as one mechanism of action. [114] Atherosclerosis is a chronic syndrome affecting the function of blood vessels including those that supply the brain. Atherosclerosis impairs cerebral blood flow and neurovascular coupling leading to cerebrovascular dysfunction. [115] Neurovascular dysfunction can occur before the onset of VaD and can eventually lead to dysregulation of cerebral blood flow (CBF) and BBB damage, followed by the activation of microglia and an inflammatory environment in the brain. [116] Cerebral blood flow is necessary to both nourish the neurons with oxygen and with glucose as well as the quick and efficient removal of carbon dioxide and waste products. In order to maintain CBF, neurons communicate with endothelial cells via neurovascular signaling pathways called the neurovascular Unit (NVU). The NVU regulates local blood vessel diameter to reflect real-time neuronal activity through neurovascular coupling. [117] A single astrocyte can contact capillaries to provide a cellular link between neuronal activity and blood vessels, termed neurovascular coupling. [118]

Excess dietary SFAs, via AS, increase pathological changes to the NVU and the cerebrovascular endothelium. This impairs the signaling pathways necessary for neurovascular coupling. Impaired neurovascular coupling can lead to brain pathologies ranging from subtle cognitive deficits to severe dementia. [119] Cerebrovascular disease affects multiple cell types within the NVU, including brain vascular cells (endothelial cells, pericytes, and vascular smooth muscle cells) and glial cells (astrocytes and microglia). Pericytes contribute to the regulation of blood flow to neurons by controlling capillary diameter, and reduction of pericytes is correlated with BBB disruption. [120] Ischemic cerebrovascular disease raises inflammatory mediators such as TNF-α, NF-kB, reactive oxygen species, tumor growth factor-β, IL-1, IL-6 and other cytokines. [121]

The neurovascular unit involves an interaction between neurons, glial cells, and cerebrovascular endothelial cells. This dynamic NVU is needed for communication and fine regulation of CBF not only to fulfil metabolic needs, but also for brain development, nourishment, repair, and BBB functioning. Both nitric oxide and prostacyclin help control CBF to neurons. [122, 123]

8. Conclusion

Diets with low SFAs have been clearly shown to correlate with better cognition and reduced VaD, compared to diets high in SFAs. Lowered brain perfusion and reduced cognitive abilities are related to the buildup of atherosclerotic plaque. Diets with low SFAs decrease atherosclerotic plaque. Tiny strokes that contribute to VaD are a result of atherosclerotic plaque breaking off and blocking cerebral arteries. Low dietary SFAs also decrease inflammation in the brain by reducing the triggering of toll-like receptor-4, reducing activation of NF-kB, decreasing cytokines, and reducing destructive oxidative stress that can kill neurons or damage their connections. When nerve cells are active, they signal nearby arteries to deliver more glucose and oxygen, but this neurovascular coupling is inhibited by excess dietary SFAs. Reducing excess dietary SFAs is a viable and safe therapy option to improve cognition in VaD.

Compliance with ethical standards

Acknowledgments

I thank my fellow authors for their expert assistance.

Disclosure of conflict of interest

No Conflict of interest.

References

[1] Bansal S, Singh S, Sharma A. Role of reactive oxygen species (ROS) and cytokines in vascular dementia: a review. Int J Pharm Teach Pract. 2015;6(4):2620-9.

[2] Kalaria RN. The pathology and pathophysiology of vascular dementia. Neuropharmacology. 2018 May 15;134:226-39.

[3] Duong MT, Nasrallah IM, Wolk DA, Chang CC, Chang TY. Cholesterol, atherosclerosis, and APOE in vascular contributions to cognitive impairment and dementia (VCID): potential mechanisms and therapy. Frontiers in Aging Neuroscience. 2021 Mar 25;13:647990.

[4] Kalaria RN. The pathology and pathophysiology of vascular dementia. Neuropharmacology. 2018 May 15;134:226-39.

[5] Tricco AC, Ashoor HM, Soobiah C, Rios P, Veroniki AA, Hamid JS, Ivory JD, Khan PA, Yazdi F, Ghassemi M, Blondal E. Comparative effectiveness and safety of cognitive enhancers for treating Alzheimer's disease: systematic review and network metaanalysis. Journal of the American Geriatrics Society. 2018 Jan;66(1):170-8.

[6] Hu FB, Stampfer MJ, Manson JE, Rimm E, Colditz GA, Rosner BA, Hennekens CH, Willett WC. Dietary fat intake and the risk of coronary heart disease in women. New England journal of medicine. 1997 Nov 20;337(21):1491-9.

[7] Wang F, Cao Y, Ma L, Pei H, Rausch WD, Li H. Dysfunction of cerebrovascular endothelial cells: prelude to vascular dementia. Frontiers in aging neuroscience. 2018 Nov 16;10:376.

[8] Duong MT, Nasrallah IM, Wolk DA, Chang CC, Chang TY. Cholesterol, atherosclerosis, and APOE in vascular contributions to cognitive impairment and dementia (VCID): potential mechanisms and therapy. Frontiers in Aging Neuroscience. 2021 Mar 25;13:647990.

[9] Freeman LR, Haley-Zitlin V, Rosenberger DS, Granholm AC. Damaging effects of a high-fat diet to the brain and cognition: a review of proposed mechanisms. Nutritional neuroscience. 2014 Nov 1;17(6):241-51.

[10] Harrison S, Brassard D, Lemieux S, Lamarche B. Consumption and sources of saturated fatty acids according to the 2019 Canada Food Guide: data from the 2015 Canadian Community Health Survey. Nutrients. 2019 Aug 21;11(9):1964.

[11] Freeman LR, Haley-Zitlin V, Rosenberger DS, Granholm AC. Damaging effects of a high-fat diet to the brain and cognition: a review of proposed mechanisms. Nutritional neuroscience. 2014 Nov 1;17(6):241-51.

[12] Haast RA, Kiliaan AJ. Impact of fatty acids on brain circulation, structure and function. Prostaglandins, Leukotrienes and Essential Fatty Acids. 2015 Jan 1;92:3-14.

[13] Kalaria RN. The pathology and pathophysiology of vascular dementia. Neuropharmacology. 2018 May 15;134:226-39.

[14] Baym CL, Khan NA, Monti JM, Raine LB, Drollette ES, Moore RD, Scudder MR, Kramer AF, Hillman CH, Cohen NJ. Dietary lipids are differentially associated with hippocampal-dependent relational memory in prepubescent children. The American journal of clinical nutrition. 2014 May 1;99(5):1026-32.

[15] Meraz-Ríos MA, Leal-Galicia P. High-Fat and Cholesterol Intake Affects Brain Homeostasis and Could Accelerate the Development of Dementia: A Systemic View. InUpdate on Dementia 2016 Sep 28. IntechOpen.

[16] Takechi R, Galloway S, Pallebage-Gamarallage MM, Lam V, Mamo JC. Dietary fats, cerebrovasculature integrity and Alzheimer's disease risk. Progress in lipid research. 2010 Apr 1;49(2):159-70.

[17] Wang F, Cao Y, Ma L, Pei H, Rausch WD, Li H. Dysfunction of cerebrovascular endothelial cells: prelude to vascular dementia. Frontiers in aging neuroscience. 2018 Nov 16;10:376.

[18] Yamazaki Y, Kanekiyo T. Blood-brain barrier dysfunction and the pathogenesis of Alzheimer's disease. International journal of molecular sciences. 2017 Sep 13;18(9):1965.

[19] Kotlęga D, Peda B, Palma J, Zembroń-Łacny A, Gołąb-Janowska M, Masztalewicz M, Nowacki P, Szczuko M. Free Fatty Acids Are Associated with the Cognitive Functions in Stroke Survivors. International Journal of Environmental Research and Public Health. 2021 Jun 16;18(12):6500.

[20] Skoog I, Korczyn AD, Guekht A. Neuroprotection in vascular dementia: a future path. Journal of the neurological sciences. 2012 Nov 15;322(1-2):232-6.

[21] Kellar D, Craft S. Brain insulin resistance in Alzheimer's disease and related disorders: mechanisms and therapeutic approaches. The Lancet Neurology. 2020 Sep 1;19(9):758-66. .

[22] Bayer-Carter JL, Green PS, Montine TJ, VanFossen B, Baker LD, Watson GS, Bonner LM, Callaghan M, Leverenz JB, Walter BK, Tsai E. Diet intervention and cerebrospinal fluid biomarkers in amnestic mild cognitive impairment. Archives of neurology. 2011 Jun 13;68(6):743-52.

[23] Hanson AJ, Craft S. The Impact of High Saturated Fat and High Glycemic Index Foods on Cognitive Function and Alzheimer's Disease Biomarkers: Does a Typical Western Diet Cause Alzheimer's Disease?. InDiet and Nutrition in Dementia and Cognitive Decline 2015 Jan 1 (pp. 733-742). Academic Press.

[24] Kris-Etherton PM, Petersen K, Van Horn L. Convincing evidence supports reducing saturated fat to decrease cardiovascular disease risk. BMJ Nutrition, Prevention & Health. 2018;1(1):23.

[25] Francis HM, Stevenson RJ. Higher reported saturated fat and refined sugar intake is associated with reduced hippocampal-dependent memory and sensitivity to interoceptive signals. Behavioral neuroscience. 2011 Dec;125(6):943.

[26] Taylor ZB, Stevenson RJ, Ehrenfeld L, Francis HM. The impact of saturated fat, added sugar and their combination on human hippocampal integrity and function: A systematic review and meta-analysis. Neuroscience & Biobehavioral Reviews. 2021 Nov 1;130:91-106.

[27] Cholerton BR, Baker LD, Craft SU. Insulin resistance and pathological brain ageing. Diabetic Medicine. 2011 Dec;28(12):1463-75.

[28] Hanson AJ, Craft S. The Impact of High Saturated Fat and High Glycemic Index Foods on Cognitive Function and Alzheimer's Disease Biomarkers: Does a Typical Western Diet Cause Alzheimer's Disease?. InDiet and Nutrition in Dementia and Cognitive Decline 2015 Jan 1 (pp. 733-742). Academic Press.

[29] Freeman LR, Haley-Zitlin V, Rosenberger DS, Granholm AC. Damaging effects of a high-fat diet to the brain and cognition: a review of proposed mechanisms. Nutritional neuroscience. 2014 Nov 1;17(6):241-51.

[30] Wahl D, Solon-Biet SM, Cogger VC, Fontana L, Simpson SJ, Le Couteur DG, Ribeiro RV. Aging, lifestyle and dementia. Neurobiology of disease. 2019 Oct 1;130:104481.

[31] McLean FH, Grant C, Morris AC, Horgan GW, Polanski AJ, Allan K, Campbell FM, Langston RF, Williams LM. Rapid and reversible impairment of episodic memory by a high-fat diet in mice. Scientific reports. 2018 Aug 10;8(1):1-9.

[32] Pistell PJ, Morrison CD, Gupta S, Knight AG, Keller JN, Ingram DK, Bruce-Keller AJ. Cognitive impairment following high fat diet consumption is associated with brain inflammation. Journal of neuroimmunology. 2010 Feb 26;219(1-2):25-32.

[33] Rogers RL, Meyer JS, McClintic K, Mortel KF. Reducing hypertriglyceridemia in elderly patients with cerebrovascular disease stabilizes or improves cognition and cerebral perfusion. Angiology. 1989 Apr;40(4):260-9.

[34] Fan R, Zhao L, Ding BJ, Xiao R, Ma WW. The association of blood non-esterified fatty acid, saturated fatty acids, and polyunsaturated fatty acids levels with mild cognitive impairment in Chinese population aged 35–64 years: a cross-sectional study. Nutritional Neuroscience. 2021 Feb 1;24(2):148-60.

[35] Tuck NJ, Farrow CV, Thomas JM. Frequency of fruit consumption and savoury snacking predict psychological health; selective mediation via cognitive failures. British Journal of Nutrition. 2022 May 26:1-0.

[36] Kalmijn S, Launer LJ, Ott A, Witteman JC, Hofman A, Breteler MM. Dietary fat intake and the risk of incident dementia in the Rotterdam Study. Annals of neurology. 1997 Nov;42(5):776-82.

[37] Edwards LM, Murray AJ, Holloway CJ, Carter EE, Kemp GJ, Codreanu I, Brooker H, Tyler DJ, Robbins PA, Clarke K. Short-term consumption of a high-fat diet impairs whole-body efficiency and cognitive function in sedentary men. The FASEB journal. 2011 Mar;25(3):1088-96.

[38] Holloway CJ, Cochlin LE, Emmanuel Y, Murray A, Codreanu I, Edwards LM, Szmigielski C, Tyler DJ, Knight NS, Saxby BK, Lambert B. A high-fat diet impairs cardiac high-energy phosphate metabolism and cognitive function in healthy human subjects. The American journal of clinical nutrition. 2011 Apr 1;93(4):748-55.

[39] Haast RA, Kiliaan AJ. Impact of fatty acids on brain circulation, structure and function. Prostaglandins, Leukotrienes and Essential Fatty Acids. 2015 Jan 1;92:3-14.

[40] Okereke OI, Rosner BA, Kim DH, Kang JH, Cook NR, Manson JE, Buring JE, Willett WC, Grodstein F. Dietary fat types and 4-year cognitive change in community-dwelling older women. Annals of neurology. 2012 Jul;72(1):124-34.

[41] Eskelinen MH, Ngandu T, Helkala EL, Tuomilehto J, Nissinen A, Soininen H, Kivipelto M. Fat intake at midlife and cognitive impairment later in life: a population-based CAIDE study. International Journal of Geriatric Psychiatry: A journal of the psychiatry of late life and allied sciences. 2008 Jul;23(7):741-7.

[42] Baym CL, Khan NA, Monti JM, Raine LB, Drollette ES, Moore RD, Scudder MR, Kramer AF, Hillman CH, Cohen NJ. Dietary lipids are differentially associated with hippocampal-dependent relational memory in prepubescent children. The American journal of clinical nutrition. 2014 May 1;99(5):1026-32.

[43] Ruan Y, Tang J, Guo X, Li K, Li D. Dietary fat intake and risk of Alzheimer's disease and dementia: a meta-analysis of cohort studies. Current Alzheimer Research. 2018 Aug 1;15(9):869-76.

[44] Kouvari M, D'Cunha NM, Travica N, Sergi D, Zec M, Marx W, Naumovski N. Metabolic Syndrome, Cognitive Impairment and the Role of Diet: A Narrative Review. Nutrients. 2022 Jan 13;14(2):333.

[45] Solfrizzi, V. 2011. Handbook of Behavior, Food and Nutrition, DOI 10.1007/978-0-387-92271-3_179.

[46] Baym CL, Khan NA, Monti JM, Raine LB, Drollette ES, Moore RD, Scudder MR, Kramer AF, Hillman CH, Cohen NJ. Dietary lipids are differentially associated with hippocampal-dependent relational memory in prepubescent children. The American journal of clinical nutrition. 2014 May 1;99(5):1026-32.

[47] Wahl D, Solon-Biet SM, Cogger VC, Fontana L, Simpson SJ, Le Couteur DG, Ribeiro RV. Aging, lifestyle and dementia. Neurobiology of disease. 2019 Oct 1;130:104481.

[48] Oleson S, Gonzales MM, Tarumi T, Davis JN, Cassill CK, Tanaka H, Haley AP. Nutrient intake and cerebral metabolism in healthy middle-aged adults: Implications for cognitive aging. Nutritional neuroscience. 2017 Sep 14;20(8):489-96.

[49] Morris MC, Tangney CC. Dietary fat composition and dementia risk. Neurobiology of aging. 2014 Sep 1;35:S59-64.

[50] Zhu RZ, Chen MQ, Zhang ZW, Wu TY, Zhao WH. Dietary fatty acids and risk for Alzheimer's disease, dementia, and mild cognitive impairment: A prospective cohort meta-analysis. Nutrition. 2021 Oct 1;90:111355.

[51] Kanoski SE, Davidson TL. Western diet consumption and cognitive impairment: links to hippocampal dysfunction and obesity. Physiology & behavior. 2011 Apr 18;103(1):59-68.

[52] Freeman LR, Haley-Zitlin V, Rosenberger DS, Granholm AC. Damaging effects of a high-fat diet to the brain and cognition: a review of proposed mechanisms. Nutritional neuroscience. 2014 Nov 1;17(6):241-51.

[53] Ahmad MA, Kareem O, Khushtar M, Akbar M, Haque MR, Iqubal A, Haider MF, Pottoo FH, Abdulla FS, Al-Haidar MB, Alhajri N. Neuroinflammation: A Potential Risk for Dementia. International Journal of Molecular Sciences. 2022 Jan 6;23(2):616.

[54] Morris MC, Evans DA, Tangney CC, Bienias JL, Schneider JA, Wilson RS, Scherr PA. Dietary copper and high saturated and trans fat intakes associated with cognitive decline. Archives of neurology. 2006 Aug 1;63(8):1085-8.

[55] Pistell PJ, Morrison CD, Gupta S, Knight AG, Keller JN, Ingram DK, Bruce-Keller AJ. Cognitive impairment following high fat diet consumption is associated with brain inflammation. Journal of neuroimmunology. 2010 Feb 26;219(1-2):25-32.

[56] Eskelinen MH, Ngandu T, Helkala EL, Tuomilehto J, Nissinen A, Soininen H, Kivipelto M. Fat intake at midlife and cognitive impairment later in life: a population-based CAIDE study. International Journal of Geriatric Psychiatry: A journal of the psychiatry of late life and allied sciences. 2008 Jul;23(7):741-7.

[57] Attuquayefio T, Stevenson RJ, Oaten MJ, Francis HM. A four-day Western-style dietary intervention causes reductions in hippocampal-dependent learning and memory and interoceptive sensitivity. PLoS One. 2017 Feb 23;12(2):e0172645.

[58] Więckowska-Gacek A, Mietelska-Porowska A, Wydrych M, Wojda U. Western diet as a trigger of Alzheimer's disease: From metabolic syndrome and systemic inflammation to neuroinflammation and neurodegeneration. Ageing research reviews. 2021 Sep 1;70:101397.

[59] Markofski MM, Dolan CT, Davies NA, Ryan EJ, Carrillo AE. BDNF decreases in response to an 8-week "Paleo" diet intervention. Brain, Behavior, and Immunity. 2017 Nov 1;66:e38.

[60] Baym CL, Khan NA, Monti JM, Raine LB, Drollette ES, Moore RD, Scudder MR, Kramer AF, Hillman CH, Cohen NJ. Dietary lipids are differentially associated with hippocampal-dependent relational memory in prepubescent children. The American journal of clinical nutrition. 2014 May 1;99(5):1026-32.

[61] Park HR, Park M, Choi J, Park KY, Chung HY, Lee J. A high-fat diet impairs neurogenesis: involvement of lipid peroxidation and brain-derived neurotrophic factor. Neuroscience letters. 2010 Oct 4;482(3):235-9.

[62] Wu A, Ying Z, Gomez-Pinilla F. The interplay between oxidative stress and brain-derived neurotrophic factor modulates the outcome of a saturated fat diet on synaptic plasticity and cognition. European Journal of Neuroscience. 2004 Apr;19(7):1699-707.

[63] Molteni R, Barnard RJ, Ying Z, Roberts CK, Gomez-Pinilla F. A high-fat, refined sugar diet reduces hippocampal brain-derived neurotrophic factor, neuronal plasticity, and learning. Neuroscience. 2002 Jul 19;112(4):803-14.

[64] Eskelinen MH, Ngandu T, Helkala EL, Tuomilehto J, Nissinen A, Soininen H, Kivipelto M. Fat intake at midlife and cognitive impairment later in life: a population-based CAIDE study. International Journal of Geriatric Psychiatry: A journal of the psychiatry of late life and allied sciences. 2008 Jul;23(7):741-7.

[65] Solfrizzi V, Frisardi V, Capurso C, D'Introno A, Colacicco AM, Vendemiale G, Capurso A, Panza F. Dietary fatty acids in dementia and predementia syndromes: epidemiological evidence and possible underlying mechanisms. Ageing research reviews. 2010 Apr 1;9(2):184-99.

[66] Hill M, Takechi R, Chaliha DR, Albrecht MA, Wright J, James AP, Clark K, Dhaliwal SS, Lam V, Mamo JC. Dietary saturated fats and apolipoprotein B48 levels are similarly associated with cognitive decline in healthy older aged Australians. Asia Pacific Journal of Clinical Nutrition. 2020 Sep;29(3):537-44.

[67] Fan R, Zhao L, Ding BJ, Xiao R, Ma WW. The association of blood non-esterified fatty acid, saturated fatty acids, and polyunsaturated fatty acids levels with mild cognitive impairment in Chinese population aged 35–64 years: a cross-sectional study. Nutritional Neuroscience. 2021 Feb 1;24(2):148-60.

[68] Baym CL, Khan NA, Monti JM, Raine LB, Drollette ES, Moore RD, Scudder MR, Kramer AF, Hillman CH, Cohen NJ. Dietary lipids are differentially associated with hippocampal-dependent relational memory in prepubescent children. The American journal of clinical nutrition. 2014 May 1;99(5):1026-32.

[69] Beaulieu J, Costa G, Renaud J, Moitié A, Glémet H, Sergi D, Martinoli MG. The neuroinflammatory and neurotoxic potential of palmitic acid is mitigated by oleic acid in microglial cells and microglial-neuronal co-cultures. Molecular Neurobiology. 2021 Jun;58(6):3000-14

[70] Dumas JA, Bunn JY, Nickerson J, Crain KI, Ebenstein DB, Tarleton EK, Makarewicz J, Poynter ME, Kien CL. Dietary saturated fat and monounsaturated fat have reversible effects on brain function and the secretion of pro-inflammatory cytokines in young women. Metabolism. 2016 Oct 1;65(10):1582-8.

[71] Baranowski BJ, Marko DM, Fenech RK, Yang AJ, MacPherson RE. Healthy brain, healthy life: a review of diet and exercise interventions to promote brain health and reduce Alzheimer's disease risk. Applied Physiology, Nutrition, and Metabolism. 2020;45(10):1055-65.

[72] Giugliano D, Ceriello A, Esposito K. The effects of diet on inflammation: emphasis on the metabolic syndrome. Journal of the American College of Cardiology. 2006 Aug 15;48(4):677-85.

[73] Wahl D, Solon-Biet SM, Cogger VC, Fontana L, Simpson SJ, Le Couteur DG, Ribeiro RV. Aging, lifestyle and dementia. Neurobiology of disease. 2019 Oct 1;130:104481.

[74] Wang F, Cao Y, Ma L, Pei H, Rausch WD, Li H. Dysfunction of cerebrovascular endothelial cells: prelude to vascular dementia. Frontiers in aging neuroscience. 2018 Nov 16;10:376.

[75] Freeman LR, Haley-Zitlin V, Rosenberger DS, Granholm AC. Damaging effects of a high-fat diet to the brain and cognition: a review of proposed mechanisms. Nutritional neuroscience. 2014 Nov 1;17(6):241-51.

[76] Więckowska-Gacek A, Mietelska-Porowska A, Wydrych M, Wojda U. Western diet as a trigger of Alzheimer's disease: From metabolic syndrome and systemic inflammation to neuroinflammation and neurodegeneration. Ageing research reviews. 2021 Sep 1;70:101397.

[77] Freeman LR, Granholm AC. Vascular changes in rat hippocampus following a high saturated fat and cholesterol diet. Journal of Cerebral Blood Flow & Metabolism. 2012 Apr;32(4):643-53.

[78] Pistell PJ, Morrison CD, Gupta S, Knight AG, Keller JN, Ingram DK, Bruce-Keller AJ. Cognitive impairment following high fat diet consumption is associated with brain inflammation. Journal of neuroimmunology. 2010 Feb 26;219(1-2):25-32.

[79] Cooper JL. Dietary lipids in the aetiology of Alzheimer's disease. Drugs & aging. 2003 May;20(6):399-418.

[80] Duong MT, Nasrallah IM, Wolk DA, Chang CC, Chang TY. Cholesterol, atherosclerosis, and APOE in vascular contributions to cognitive impairment and dementia (VCID): potential mechanisms and therapy. Frontiers in Aging Neuroscience. 2021 Mar 25;13:647990.

[81] Freeman LR, Haley-Zitlin V, Rosenberger DS, Granholm AC. Damaging effects of a high-fat diet to the brain and cognition: a review of proposed mechanisms. Nutritional neuroscience. 2014 Nov 1;17(6):241-51.

[82] Więckowska-Gacek A, Mietelska-Porowska A, Wydrych M, Wojda U. Western diet as a trigger of Alzheimer's disease: From metabolic syndrome and systemic inflammation to neuroinflammation and neurodegeneration. Ageing research reviews. 2021 Sep 1;70:101397.

[83] Rantanen K, Strandberg AY, Salomaa V, Pitkälä K, Tilvis RS, Tienari P, Strandberg T. Cardiovascular risk factors and glucose tolerance in midlife and risk of cognitive disorders in old age up to a 49-year follow-up of the Helsinki businessmen study. Annals of Medicine. 2017 Aug 18;49(6):462-9.

[84] Solfrizzi, V. 2011. Handbook of Behavior, Food and Nutrition, DOI 10.1007/978-0-387-92271-3_179.

[85] Barnard ND, Bunner AE, Agarwal U. Saturated and trans fats and dementia: a systematic review. Neurobiology of aging. 2014 Sep 1;35:S65-73.

[86] Calder PC. Functional roles of fatty acids and their effects on human health. Journal of parenteral and enteral nutrition. 2015 Sep;39:18S-32S.

[87] Brockdorf Y, Morley JE. Nutrition and Dementia. The journal of nutrition, health & aging. 2021 May;25(5):590-2.

[88] Duong MT, Nasrallah IM, Wolk DA, Chang CC, Chang TY. Cholesterol, atherosclerosis, and APOE in vascular contributions to cognitive impairment and dementia (VCID): potential mechanisms and therapy. Frontiers in Aging Neuroscience. 2021 Mar 25;13:647990.

[89] Freeman LR, Haley-Zitlin V, Rosenberger DS, Granholm AC. Damaging effects of a high-fat diet to the brain and cognition: a review of proposed mechanisms. Nutritional neuroscience. 2014 Nov 1;17(6):241-51.

[90] Haast RA, Kiliaan AJ. Impact of fatty acids on brain circulation, structure and function. Prostaglandins, Leukotrienes and Essential Fatty Acids. 2015 Jan 1;92:3-14.

[91] Iuliano L, Micheletta F, Natoli S, Corradini SG, Iappelli M, Elisei W, Giovannelli L, Violi F, Diczfalusy U. Measurement of oxysterols and α-tocopherol in plasma and tissue samples as indices of oxidant stress status. Analytical biochemistry. 2003 Jan 15;312(2):217-23.

[92] Haast RA, Kiliaan AJ. Impact of fatty acids on brain circulation, structure and function. Prostaglandins, Leukotrienes and Essential Fatty Acids. 2015 Jan 1;92:3-14.

[93] Shabir O, Berwick J, Francis SE. Neurovascular dysfunction in vascular dementia, Alzheimer's and atherosclerosis. BMC neuroscience. 2018 Dec;19(1):1-6.

[94] Huang YT, Hong FF, Yang SL. Atherosclerosis: The Culprit and Co-victim of Vascular Dementia. Frontiers in Neuroscience. 2021;15.

[95] Duong MT, Nasrallah IM, Wolk DA, Chang CC, Chang TY. Cholesterol, atherosclerosis, and APOE in vascular contributions to cognitive impairment and dementia (VCID): potential mechanisms and therapy. Frontiers in Aging Neuroscience. 2021 Mar 25;13:647990.

[96] Yamazaki Y, Kanekiyo T. Blood-brain barrier dysfunction and the pathogenesis of Alzheimer's disease. International journal of molecular sciences. 2017 Sep 13;18(9):1965.

[97] Yang Y, Yao JJ, Du JL, Bai R, Sun LP, Sun GH, Song GR, Cao SM, Shi CH, Ba Y, Xing Q. Primary prevention of macroangiopathy in patients with short-duration type 2 diabetes by intensified multifactorial intervention: seven-year follow-up of diabetes complications in Chinese. Diabetes Care. 2013 Apr 1;36(4):978-84.

[98] Oviedo DC, Lezcano H, Perez AR, Villarreal AE, Carreira MB, Isaza B, Wesley L, Grajales SA, Fernandez S, Frank A, Britton GB. Vascular biomarkers and ApoE4 expression in mild cognitive impairment and Alzheimer's disease. AIMS neuroscience. 2018;5(2):148.

[99] Balestrini S, Perozzi C, Altamura C, Vernieri F, Luzzi S, Bartolini M, Provinciali L, Silvestrini M. Severe carotid stenosis and impaired cerebral hemodynamics can influence cognitive deterioration. Neurology. 2013 Jun 4;80(23):2145-50.

[100] Yue W, Shi Z, Zhang M, Liu S, Liu S, Zhang T, Tong X, Zhou Y, Ji Y. Cognitive outcome after carotid artery stenting in patients with cerebral ischemia. Biomedical Research (0970-938X). 2016 Apr 1;27(2).

[101] Huang YT, Hong FF, Yang SL. Atherosclerosis: The Culprit and Co-victim of Vascular Dementia. Frontiers in Neuroscience. 2021;15.

[102] Duong MT, Nasrallah IM, Wolk DA, Chang CC, Chang TY. Cholesterol, atherosclerosis, and APOE in vascular contributions to cognitive impairment and dementia (VCID): potential mechanisms and therapy. Frontiers in Aging Neuroscience. 2021 Mar 25;13:647990.

[103] Huang YT, Hong FF, Yang SL. Atherosclerosis: The Culprit and Co-victim of Vascular Dementia. Frontiers in Neuroscience. 2021;15.

[104] Duong MT, Nasrallah IM, Wolk DA, Chang CC, Chang TY. Cholesterol, atherosclerosis, and APOE in vascular contributions to cognitive impairment and dementia (VCID): potential mechanisms and therapy. Frontiers in Aging Neuroscience. 2021 Mar 25;13:647990.

[105] Wang X, Zhang B, Xia R, Jia QY. Inflammation, apoptosis and autophagy as critical players in vascular dementia. Eur Rev Med Pharmacol Sci. 2020 Sep 1;24(18):9601-14.

[106] Hoscheidt SM, Sanderlin AH, Baker LD, Jung Y, Whitlow CT, Hanson AJ, Wittmer P, Sink KM, Friedman S, Craft S. P2-358: A diet high in saturated fat and simple carbohydrates reduces cerebral perfusion and increases levels of cerebrospinal fluid ab42: a randomized trial. Alzheimer's & Dementia. 2018 Jul;14(7S_Part_15):P826-7.

[107] Huang YT, Hong FF, Yang SL. Atherosclerosis: The Culprit and Co-victim of Vascular Dementia. Frontiers in Neuroscience. 2021;15.

[108] Gustavsson AM, Van Westen D, Stomrud E, Engström G, Nägga K, Hansson O. Midlife atherosclerosis and development of Alzheimer or vascular dementia. Annals of neurology. 2020 Jan;87(1):52-62.

[109] Anstey KJ, Ashby-Mitchell K, Peters R. Updating the evidence on the association between serum cholesterol and risk of late-life dementia: review and meta-analysis. Journal of Alzheimer's disease. 2017 Jan 1;56(1):215-28.

[110] Huang YT, Hong FF, Yang SL. Atherosclerosis: The Culprit and Co-victim of Vascular Dementia. Frontiers in Neuroscience. 2021;15.

[111] Gustavsson AM, Van Westen D, Stomrud E, Engström G, Nägga K, Hansson O. Midlife atherosclerosis and development of Alzheimer or vascular dementia. Annals of neurology. 2020 Jan;87(1):52-62.

[112] Huang YT, Hong FF, Yang SL. Atherosclerosis: The Culprit and Co-victim of Vascular Dementia. Frontiers in Neuroscience. 2021;15.

[113] Guerchet M, Aboyans V, Nubukpo P, Lacroix P, Clément JP, Preux PM. Ankle-brachial index as a marker of cognitive impairment and dementia in general population. A systematic review. Atherosclerosis. 2011 Jun 1;216(2):251-7.

[114] Haast RA, Kiliaan AJ. Impact of fatty acids on brain circulation, structure and function. Prostaglandins, Leukotrienes and Essential Fatty Acids. 2015 Jan 1;92:3-14.

[115] Shabir O, Berwick J, Francis SE. Neurovascular dysfunction in vascular dementia, Alzheimer's and atherosclerosis. BMC neuroscience. 2018 Dec;19(1):1-6.

[116] Wang F, Cao Y, Ma L, Pei H, Rausch WD, Li H. Dysfunction of cerebrovascular endothelial cells: prelude to vascular dementia. Frontiers in aging neuroscience. 2018 Nov 16;10:376.

[117] Duong MT, Nasrallah IM, Wolk DA, Chang CC, Chang TY. Cholesterol, atherosclerosis, and APOE in vascular contributions to cognitive impairment and dementia (VCID): potential mechanisms and therapy. Frontiers in Aging Neuroscience. 2021 Mar 25;13:647990.

[118] Yamazaki Y, Kanekiyo T. Blood-brain barrier dysfunction and the pathogenesis of Alzheimer's disease. International journal of molecular sciences. 2017 Sep 13;18(9):1965.

[119] Shabir O, Berwick J, Francis SE. Neurovascular dysfunction in vascular dementia, Alzheimer's and atherosclerosis. BMC neuroscience. 2018 Dec;19(1):1-6.

[120] Yamazaki Y, Kanekiyo T. Blood-brain barrier dysfunction and the pathogenesis of Alzheimer's disease. International journal of molecular sciences. 2017 Sep 13;18(9):1965.

[121] Bansal S, Singh S, Sharma A. Role of reactive oxygen species (ROS) and cytokines in vascular dementia: a review. Int J Pharm Teach Pract. 2015;6(4):2620-9.

[122] Wang F, Cao Y, Ma L, Pei H, Rausch WD, Li H. Dysfunction of cerebrovascular endothelial cells: prelude to vascular dementia. Frontiers in aging neuroscience. 2018 Nov 16;10:376.

[123] Blake, SM. Fats and Oils Demystified. Hawaii, USA: LifeLong Press; 2017., www.drsteveblake.com.