Nutrition and Dementia: A Clinical Update

Abstract

While prospective epidemiologic studies have provided strong evidence linking higher intakes of many nutrients with slower rates of cognitive decline and reduced dementia risk, randomized controlled trials on supplementation with individual nutrients have largely been disappointing. In contrast, recent research points to substantial benefits for brain aging and cognition from consumption of a varied diet centred on plant-source foods, whole grains and fish, and avoidance of foods rich in saturated and trans fats. An unhealthy dietary pattern, in conjunction with obesity, low physical activity, and smoking, could contribute to a pro-inflammatory state and oxidative stress which could exacerbate risk for development of cognitive decline the metabolic syndrome, diabetes, and cardiovascular disease.

Keywords: *nutrition, dementia, Alzheimer's disease, nutrients, dietary patterns*

Forum

Pre-test CME Quiz

Suboptimal diets[1] and diet-related metabolic diseases (e.g., diabetes, hypercholesterolemia, hypertension, metabolic syndrome) have clearly been established as risk factors for cognitive decline and dementia (see Figure 1).[2] The higher prevalence and clustering of these risk factors in obese individuals raises additional concern for the cognitive health of our current and future aging population as obesity prevalence rises. The adverse cognitive effects of obesity are already apparent in a middle-aged First Nations Canadian population,[3] perhaps as a consequence of the early age of obesity

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onset in this population.

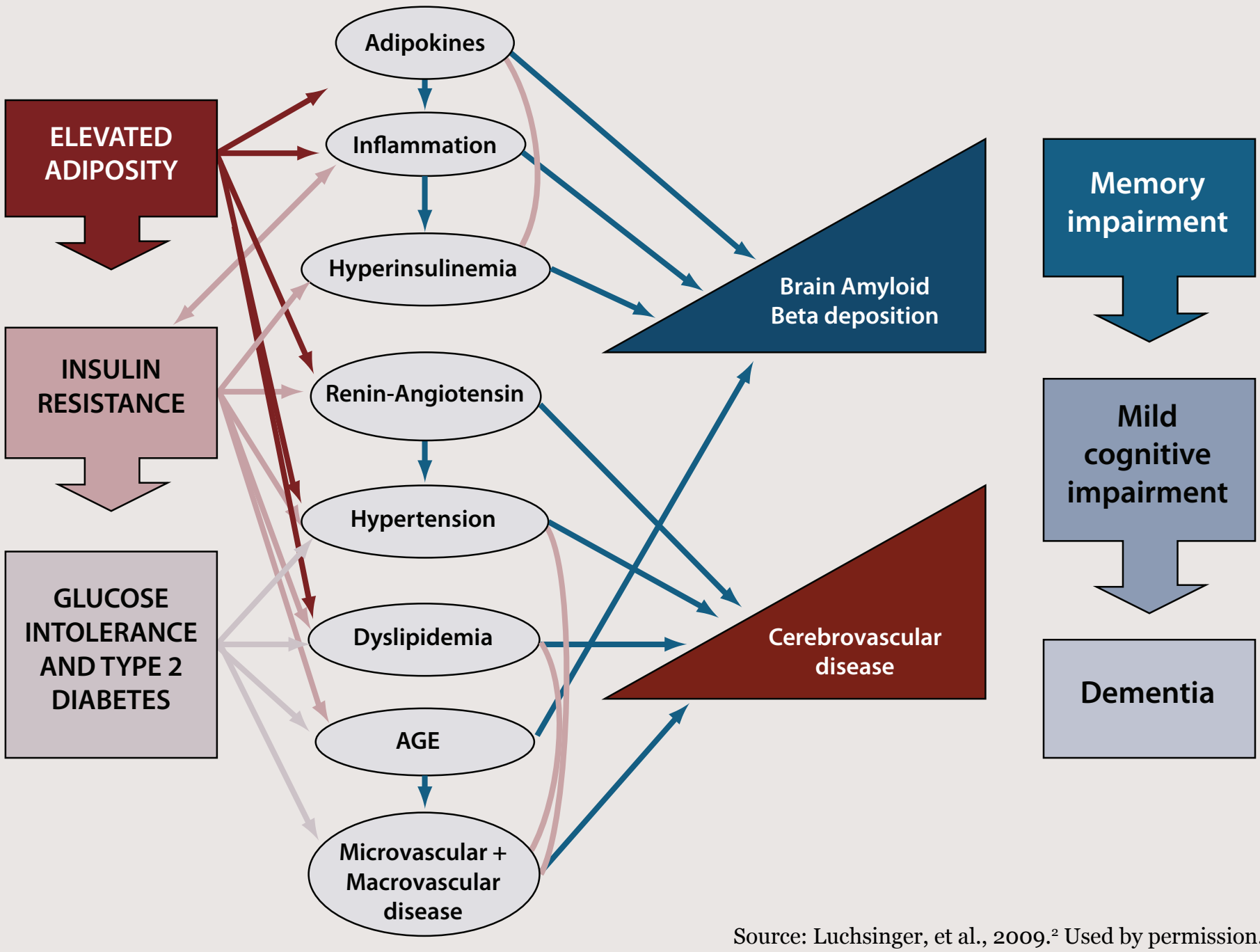
Much of the evidence in this field comes from prospective epidemiological studies, with only a handful of largely unsuccessful randomized, clinical trials (RCTs) to date. In this review, we put these findings into perspective by first addressing individual nutrients, and then turning to a broader consideration of diet patterns and overall diet quality and cognitive health.

Role of Individual Nutrients

Fat

In general, inappropriate fat intake, both quantity and quality, are implicated, with higher intakes of total, saturated and trans fats being associated with greater cognitive decline[4–7] and dementia risk, particularly Alzheimer disease (AD).[8,9] Conversely, higher intakes of monounsaturated fatty acids (MUFA), and polyunsaturated

Figure 1: Risk factors for cognitive decline and dementia



Source: Luchsinger, et al., 2009.[2] Used by permission.

fatty acids (PUFA; omega-6 and omega-3 FA) are associated with better cognitive function.[7,10,11] An individual's genotype may have a moderating influence as the association between higher fat intake and increased dementia risk was only apparent in participants with the ApoE4 genotype[12,13] in those studies where genotyping was conducted.

Regular fish consumption (rich in long-chain omega-3 FA) has been associated with decreased AD risk in several European and American longitudinal studies[8,14–16] with some studies[14,15] reporting benefits from consumption of as little as one fish meal a week. Numerous biologic roles are proposed for the long chain omega-3 FAs, including their abilities to limit oxidative stress and neuroinflammation.[17,18] However, the few RCTs completed thus far have not shown benefits for slowing the rate of cognitive decline, treating AD, or slowing the progression of any forms of dementia, although post-hoc exploratory analyses have noted marginal positive effects in small subgroups of patients with mild cognitive impairment (MCI) or mild AD.[17,19]

Key Point

Lifestyle changes, including diet, should be implemented as young as possible to help prevent obesity-associated diseases which are, in turn, risk factors for cognitive decline and dementia.

The B Vitamins

Low intakes of folate, vitamins B12 and B6 have received much interest, in part due to their link with elevated levels of homocysteine (Hcy), when these vitamins are consumed in insufficient quantities. Lower intakes and/or plasma levels of these vitamins, along with elevated Hcy, are associated with AD and vascular dementias[20,21]; this is likely related to the adverse effect of elevated Hcy levels on vascular health. Hyperhomocyteinaemia is a risk factor for vascular[22] and white matter[23] diseases, and elevated Hcy has been linked to amyloid pathology in human cell culture systems[24] and animal models.[25] Numerous RCTs of these B vitamins have been conducted[26] in an attempt to lower Hcy and slow the rate of cognitive decline. A meta-analysis of published trials[27] concluded that dietary supplementation with B vitamins had no beneficial effects among individuals with normal or impaired cognition, although as pointed out by the authors, few studies had sufficient size or duration to assess their effect on cognitive decline. An exception was the Folic Acid and Carotid Intima-Media Thickness (FACIT) trial[28] in which older participants randomly assigned to receive 0.8 mg of folic acid for 3 years experienced improved cognitive domains of memory, information processing speed, and sensorimotor speed. Since publication of this review, results from an 18-month supplementation trial with high-dose folic acid (5 mg/d), vitamin B6 (25 mg/d) and vitamin B12 (1 mg/d) conducted in individuals with mild to moderate AD and normal folic

acid, B12 and Hcy levels, were published. This regimen could not slow the rate of cognitive decline in this group of individuals.[29]

OXIDATIVE STRESS IS ONE OF THE EARLIEST EVENTS IN THE NEUROLOGICAL AND PATHOLOGICAL CHANGES IN AD[31]...

Antioxidants

Oxidative stress is one of the earliest events in the neurological and pathological changes in AD[30] and has been shown to lead to the irreversible aggregation of beta-amyloid and consequent neuronal degeneration in AD.[31] In view of their antioxidant properties, compounds such as vitamins E, C, carotenoids, polyphenols (flavonoids), and minerals such as zinc, selenium, and manganese (cofactors of enzymes superoxide dismutase and glutathione peroxidase) could help limit oxidative damage. While results have been somewhat inconsistent (e.g., Laurin et al., 2002[32]), prospective studies have generally shown that higher antioxidant intakes from foods or supplements, i.e,. vitamins E, C, or multivitamins confer protective cognitive effects. (e.g., Engelhart et al., 2002[33]; see Gillette-Guyonnet 2007 for a review[34]). However, as observed for other nutrients, RCTs of antioxidants, singly or combined, have not been encouraging, with the great majority reporting no beneficial effects. In fact, some of the trials raised a safety issue, which was identified in a meta-analysis published in 2007. In their review, Bjelakovic et al.,[35] concluded that treatment with beta-carotene, and vitamins A and E may increase mortality, with the potential impact of vitamin C and selenium needing further study.

Vitamin K

Historically known for its role in blood coagulation, vitamin K (VitK) has recently emerged as a potentially important nutrient for brain function. Animal studies show that MK-4—the principal K vitamin in the brain—is strongly correlated to certain brain sphingolipids and that rats maintained on a low VitK diet throughout their lives show signs of cognitive deficits in old age when subjected to spatial memory learning tasks.[36,37] Evidence was also provided for a protective role for MK-4 in the aging retina.[38] Whether marginal status for VitK is detrimental to brain function remains unexplored; however, one study showed that community-dwelling patients with early-stage AD had lower VitK intakes compared to age- and sex-matched cognitively intact controls.[39] As the role of VitK in the brain continues to be investigated, the potentially detrimental impact of suboptimal VitK status in brain function should be appreciated in light of the large proportion of older adults being

Key Point

Fish should be included as a protein source one to three times per week, as a main dish item, in a sandwich (e.g. salmon sandwich), in salads, or as part of mixed dishes.

treated with the anticoagulant drug warfarin (coumadin). Warfarin, a potent anti-vitamin K agent, was among the 50 most prescribed drugs in Canada in 2008[40] while almost 20 million prescriptions are written for warfarin each year in the US.[41] Whether chronic use of warfarin increases risk of dementia remains unexplored.

Summary of Individual Nutrient Studies

Prospective epidemiologic studies demonstrate slower rates of cognitive decline and reduced dementia risk in individuals with higher intakes of many individual nutrients, yet positive RCTs on supplementation with individual nutrients are not available. Several factors may account for the lack of consistency. The first relates to exposure periods. Whereas epidemiologic studies often capture intakes over several years, RCTs are substantially shorter in duration. Second, emerging evidence suggests that metabolic factors, such as obesity at middle age, are strong predictors of dementia risk.[42] Thus the protective effects of nutrients, especially as factors offsetting the neuropathologic development associated with chronic obesity-associated diseases, may be best implemented at middle, rather than older, age. Thus, the age of participants in current RCTs may simply not be consistent with the age group most likely to benefit from the trial parameters. Finally, nutrient intake estimated in epidemiologic studies is assessed from foods reported by study respondents who may have suboptimal diets. Consequently, associations between low intakes of certain foods or nutrients and greater risk of cognitive decline may reflect overall poorer quality diets rather than the inadequate intakes of single nutrients. This also accounts for the fact that single nutrients frequently exert their action in synergy with other nutrients. For example, dietary sources of both vitamin E and omega-3 FA limit oxidative stress within cell membranes. Neuroprotection is afforded by a number of metabolic pathways and not reliant on only single pathways that would be protected by individual nutrients. This underlying reality is best addressed by examining outcomes from studies that conduct analyses at the level of foods and the global diet.

Key Point

Most Canadians need to increase their vegetable intake, including a wide variety of vegetables, especially those that are darkly coloured, as these vegetables tend to have high polyphenol and vit K contents and antioxidant properties. Increase vegetable intake by including vegetable-based soups and juices in your diet.

Role of Foods and Diet Quality

Increasingly, dietary patterns and global diet quality are being investigated as factors in the prevalence or incidence of AD.[43,44] Such approaches for modelling chronic disease risk have the potential to elucidate the role of the whole diet and specific beneficial dietary patterns in preventing cognitive decline or slowing the progression from MCI to AD.

In the French 3-City (3C) cohort study that followed over 8,000 participants age 65 years

and older for 5 years, three healthy dietary patterns were characterised using a brief food frequency questionnaire (FFQ). These included weekly fish intake, daily consumption of fruits and vegetables, and use of omega-3 fatty acid-rich oils such as colza, walnut, or soya. Frequent consumption of fish (at least weekly), fruit and vegetables (daily) and regular use of omega-3 fatty acid-rich oils associated with decreased risk of developing dementia and AD, and a combination of foods providing both omega-3 fatty acids and antioxidants (fish and fruits and vegetables) conferred the best protective effect. These associations were strongest among participants who were non ApoE4 allele carriers,[16] and they were maintained when adjusted for confounding factors. Furthermore, those who had a poor diet relative to the three criteria had a greater risk of developing dementia over the follow-up period.[45] Subsequent analyses on this data set using cluster analysis to derive dietary patterns showed that a healthy dietary pattern (higher consumption of fish in men, and fruits and vegetables in women) was related to better cognitive performance in both sexes.[46]

...THOSE WHO HAD A POOR DIET RELATIVE TO THE THREE CRITERIA HAD A GREATER RISK OF DEVELOPING DEMENTIA OVER THE FOLLOW-UP PERIOD.

Key Point

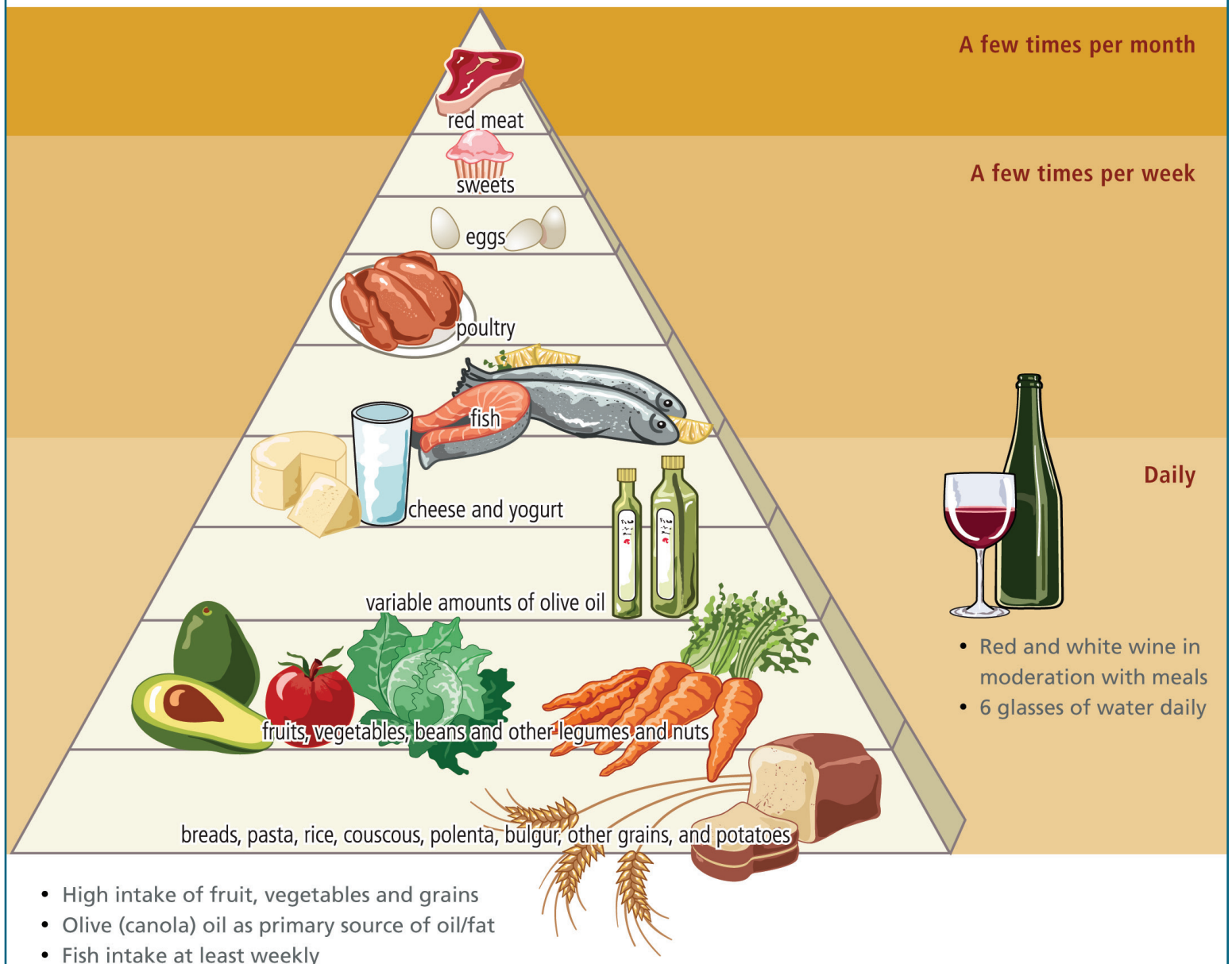
Most Canadians need to increase their intake of whole grains and legumes. Again, including legumes in soups and salads is a convenient means to increase their consumption.

The potential cognitive benefits of consuming a Mediterranean diet have been explored.[43] The Mediterranean diet is composed of fruits, vegetables, legumes, fish, whole grains, olive oil, and wine, providing dietary fibre, complex phenols, carotenoids, flavonoids, monounsaturated fats, and long-chain polyunsaturated fats such as omega-3 fatty acids and nutrients with antioxidant properties, such as vitamins E and C (see Figure 2).[47] These substances have been shown to have neuroprotective effects,[48] most likely through their action on reducing oxidative stress and inflammation.[43,47] Greater adherence to the Mediterranean diet has been associated with slower rates of cognitive decline in a French cohort living in the Bordeaux region,[49] and in an American community-dwelling population living in Chicago[50] and lower risk of AD[43] and progression of MCI to AD,[51] in a New York City based cohort.

Other global diet quality indices such as the USDA HEI (Healthy Eating Index),[52,53] the Recommended Food Score (RFS)[54] and the Healthy Diet Indicator,[55] show similar associations between higher quality diets and better retention of cognitive function.[55,56] These indices assess the extent to which participants adhere to theoretical criteria of nutritional health, based on findings from previous research or national dietary guidance such

as that provided by Canada's Food Guide (CFG, Health Canada, 2007) (see Figure 3). Canada's Food Guide recommends consumption of a varied, balanced diet based on foods that are part of a healthy eating pattern, in amounts that provide essential nutrients, and reduce the risk of obesity and chronic diseases such as type 2 diabetes, heart disease, certain types of cancer and osteoporosis. In France, the SU.VI.MAX study used an index based on the French dietary guidelines (PNNS) and showed that better PNNS guideline scores were related to higher scores on memory and verbal fluency tests.[57] Data-driven statistical techniques such as cluster analysis in a European population have also demonstrated that the "healthy diet cluster" shows a protective association with cognitive function, mood, and self-rated health.[58] Taken together, this body of research points to substantial benefits for brain aging and cognition from consumption of a varied diet centred on plant-source foods, whole grains, and fish,[1,45] and avoid-

Figure 2: The Mediterranean Diet



ance of foods rich in saturated and trans fats (baked goods and hydrogenated oils) with the potential to raise blood cholesterol.[9,12] An unhealthy dietary pattern, in conjunction with obesity, physical inactivity, and smoking, could also contribute to a pro-inflammatory state and oxidative stress which could exacerbate risk for development of cognitive decline the metabolic syndrome, diabetes, and cardiovascular disease.[46] Although still underexplored, emerging evidence thus suggests that certain lifestyle attributes, such as physical activity and consumption of a varied, high-quality diet, may have independent benefits on cognitive health,[59] justifying such global lifestyle public health promotion strategies (see Figure 4).[60]

> ...CONSUMING A HIGH-QUALITY DIET IS ASSOCIATED WITH BETTER RETENTION OF COGNITIVE HEALTH.

Summary of Food and Diet Quality Research

A number of prospective epidemiologic studies now provide evidence that consuming a high-quality diet is associated with better retention of cognitive health. However, to our knowledge, no RCTs have yet been carried out in this area to support the epidemiologic studies. This may be due to the substantial logis-

Figure 3: Canada's Food Guide

*Recommended Number of **Food Guide Servings** per Day*

	Adults			
Age in Years	19-50		51+	
Sex	Females	Males	Females	Males
Vegetables and Fruit	7-8	8-10	7	7
Grain Products	6-7	8	6	7
Milk and Alternatives	2	2	3	3
Meat and Alternatives	2	3	2	3

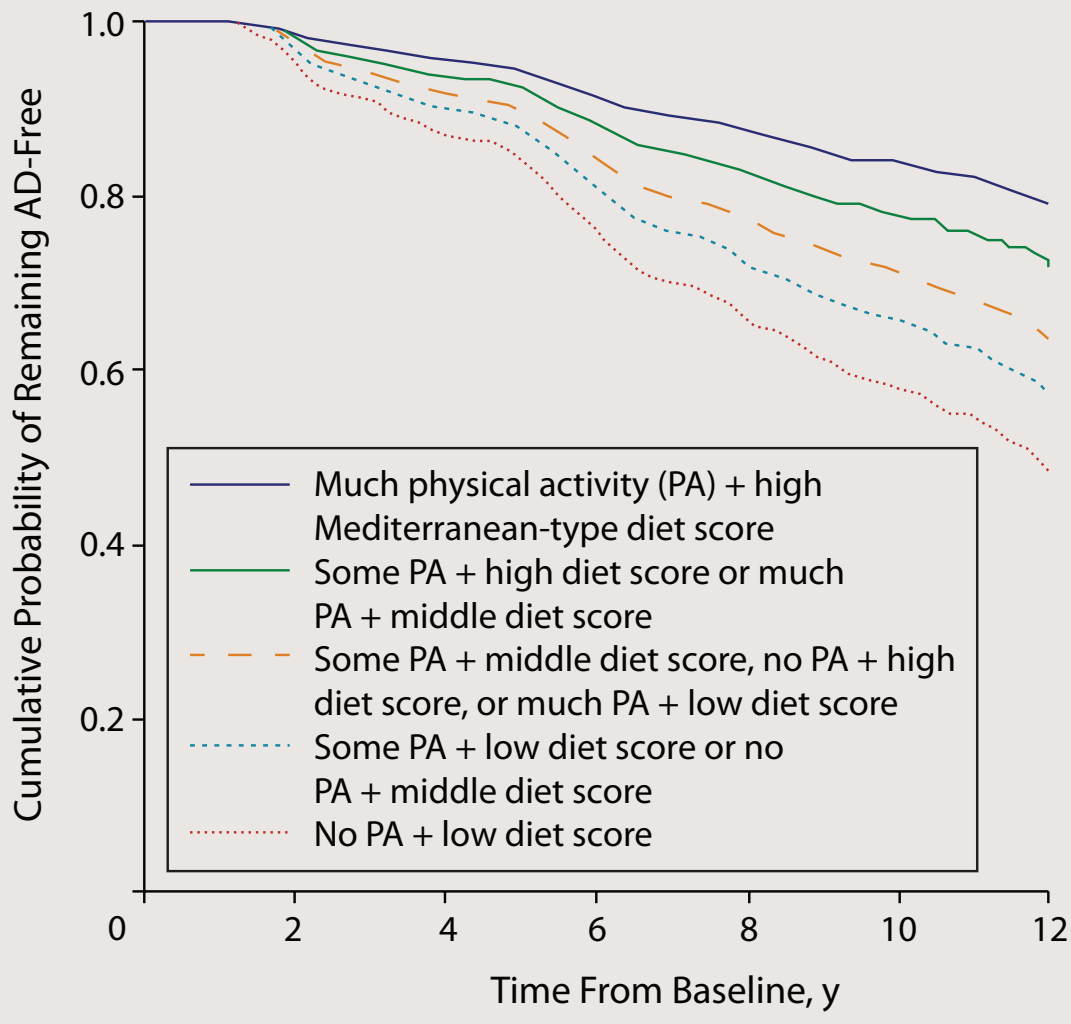
Source: Health Canada, 2007.[63]

tical challenges in ensuring and monitoring adherence to and compliance with specific dietary patterns tested in the different arms of a RCT. Currently one study has compared a measure of diet quality (USDA HEI) and adherence to the Mediterranean diet on risk of cognitive decline[50] and reported superior predictive value of Mediterranean diet adherence. Nevertheless, until this observation has been reproduced, preventive strategies based on a healthy dietary pattern could constitute a meaningful public health message for delaying cognitive decline and AD in older populations.[60]

Conclusion

Lifestyle is an important predictor of cognitive retention with aging. This article has reviewed the nutrient underpinnings of cognition and focused on the impact of beneficial foods and overall diet quality on cognitive health. While not supported by RCTs, the wealth of

Figure 4: Alzheimer's Disease Incidence in Individuals by No, Some, or Much Physical Activity and Low, Middle, and High Mediterranean-Type Diet Adherence Scores



No. at risk							
Much PA + high diet	200	192	141	60	45	35	19
Some PA + high diet or much PA + middle diet	496	470	332	135	106	73	37
Some PA + middle diet, no PA + high diet, or much PA + low diet	573	526	374	168	121	82	35
Some PA + low diet or no PA + middle diet	421	377	241	99	72	48	27
No PA + low diet	190	165	103	39	27	18	9

Source: Scarmeas N, et al, 2009. [59] Used by permission.

Summary of Key Points

Prospective epidemiologic studies have provided strong evidence for lower rates of cognitive decline and reduced dementia risk in individuals with higher intakes of many nutrients (MUFA, PUFA notably omega-3 fatty acids, folate, vitamins B12 and B6 , antioxidants) related to brain function and overall health.

Randomized controlled trials (RCTs) on supplementation with individual nutrients have largely been disappointing showing no benefits for slowing the rate of cognitive decline, treating AD, or slowing the progression of dementia.

Dietary patterns and global diet quality are increasingly being investigated as factors in the prevalence or incidence of AD.

The most recent research points to substantial benefits for brain aging and cognition from consumption of a varied diet centred on plant-source foods, whole grains and fish, and avoidance of foods rich in saturated and trans fats (baked goods and hydrogenated oils).

An unhealthy dietary pattern, in conjunction with obesity, low physical inactivity and smoking, could contribute to a pro-inflammatory state and oxidative stress which could exacerbate risk for development of cognitive decline via the metabolic syndrome, diabetes and cardiovascular disease.

Post-test CME Quiz

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epidemiologic evidence, combined with the global health benefits of healthy eating, warrant recommendation of such dietary patterns. This view is consistent with a recent report prepared for the U.S. Department of Health and Human Services[61] and the Third Canadian Consensus Conference on Diagnosis and Treatment of Dementia,[62] stating that "Although there is insufficient evidence to make a firm recommendation for the primary prevention of dementia, physicians may choose to advise their patients about the potential advantages of increased consumption of fish, reduced consumption of dietary fat and moderate consumption of wine"; it also broadens this view to encompass more global aspects of diet, including vegetables, fruits, and grains to also ensure adequate exposure to antioxidant nutrients.

No competing financial interests declared.

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Clinical Pearls

Lifestyle changes, including diet, should be implemented as young as possible to help prevent obesity-associated diseases which are, in turn, risk factors for cognitive decline and dementia.

While Canada's Food Guide provides general advice in terms of food patterns, emphasis should be placed on the following:

Fish should be included as a protein source one to three times per week, as a main dish item, in a sandwich (e.g. salmon sandwich), in salads, or as part of mixed dishes.

Most Canadians need to increase their vegetable intake, including a wide variety of vegetables, especially those that are darkly coloured as these vegetables tend to have high polyphenol and vit K contents and antioxidant properties. Increase vegetable intake by including vegetable-based soups and juices.

Most Canadians need to increase their intake of whole grains and legumes. Again, including legumes in soups and salads is a convenient means to increase their consumption.

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