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Lifestyle Approaches to Prevent and Manage Cognitive Impairment

Despite billions of dollars of research, none of the nearly 200 medications tested for dementia have been shown to stop or slow the progression of Alzheimer's disease (the most common form of memory loss). Some of these drugs help with associated symptoms of memory loss, such as anxiety, but none have offered a solution to this growing problem.

In the United States, nearly 6 million people have been diagnosed with Alzheimer's disease, and the annual bill for dementia care in 2014 was more than $215 billion, more than is spent on cancer or heart disease.[1] The number of people with the disease is expected to increase 200% by the year 2030 and increase 400% by the year 2050, to an estimated 24 million Americans with Alzheimer's disease.[2] The cost of care could exceed $1.1 trillion yearly.[2]

Currently, two urgent epidemics exist in the United States: escalating rates of disabling memory loss, along with rapidly increasing rates of diabetes and prediabetes. About 30.3 million Americans (9.4% of the U.S. population) have diabetes, 1.2 million of whom have type 1 diabetes, with rates for type 2 diabetes increasing significantly every few years.[3] As noted in the Maastricht Aging Study, people with type 2 diabetes are more likely to suffer from cognitive decline.[4] This study followed nearly 1,300 individuals 40 years of age or older for 12 years. The subjects' cognitive functions were tested three times over the course of 12 years (at the start, after six years, and then at 12 years). Those with baseline type 2 diabetes had a 300% decline in their information-processing speed compared to non-diabetics. Those with diabetes requiring insulin treatment fared even worse, with a 400% decline.

Yet, patients with diabetes are not the only ones at risk. In 2013, Crane et al showed that a fasting glucose level of 115 mg/dL compared to 100 mg/dL increased the risk for dementia by 18% ($P = 0.01$).[5] Thus, for the 86 million people in the United States with prediabetes, which is nearly one-third of the U.S. adult population and 50% of baby boomers, having a modest increase in fasting glucose levels can increase their risk for dementia.

Dr. Suzanne de la Monte was one of the first researchers to use the term type 3 diabetes for Alzheimer's disease, as her research has suggested that insulin resistance causes cognitive impairment through the effects of oxidative stress and neurodegeneration on neuronal cells.[6,7] Several other studies now have supported her initial observations that insulin resistance is linked to Alzheimer's disease.[8,9,10]

EXECUTIVE SUMMARY

Despite billions of dollars in research and nearly 200 medications tested for dementia, pharmacologic treatment for Alzheimer's disease is severely limited in effectiveness and safety. With the disappointing benefits of drug treatment, the promise of lifestyle changes to prevent and delay cognitive decline appears hopeful.

- Evidence is building for the association of diabetes and prediabetes with the development of Alzheimer's disease, with likely causative implications.
- Cognitive testing is done through the Mini-Mental State Examination and more sophisticated and sensitive tests.
- Lifestyle factors, such as greater fitness scores, lower fasting glucose levels, lower body fat, avoidance of tobacco, and moderate alcohol intake, have been associated with improved cognitive function and may slow cognitive decline.
- Studies indicate beneficial effects of aerobic exercise, avoidance of high glycemic index loads, and the intake of flavonoid-rich foods and smart fats.

Dr. Melissa Schilling from New York University outlined a second mechanism for how insulin resistance increases the risk for Alzheimer's disease. Schilling has shown how both insulin and beta-amyloid (one of the key proteins associated with Alzheimer's disease) compete for the same enzyme for their metabolism, using insulin-degrading enzyme (IDE). As there is a limited amount of IDE and as insulin levels increase, beta-amyloid breakdown is blocked, and amyloid production in the brain increases.[11] Thus, not only does insulin resistance decrease neuronal function and lead to neurodegeneration, with increased insulin levels, there is an increase in beta-amyloid formation as well.

Although insulin resistance in the brain leads to brain cell dysfunction and eventually brain cell death, body-wide insulin resistance shows other signs of dysfunction, commonly called the metabolic syndrome. Also known as Syndrome X, the diagnosis can be made if three of the five items below are present:

1. Expanding waistline (more than 40 inches in men and more than 35 inches in women);
2. High blood pressure (> 130/85 mmHg);
3. High triglycerides (≥ 150 mg/dL);
4. Low HDL cholesterol (< 40 mg/dL for men and < 50 mg/dL for women);
5. High fasting blood sugar levels (≥ 100 mg/dL; this often is the last sign to occur).

Some experts even suggest elevated inflammation, measured by a high-sensitivity C-reactive protein blood test (hs-CRP > 1), to be considered as one of the signs of metabolic syndrome.

Although this may not be warranted for clinical practice, for clinical research purposes, a tool to assess insulin resistance (IR) uses the Homeostasis Model Assessment (HOMA) that measures beta cell function and insulin sensitivity: HOMA-IR score = glucose mg/dL × insulin level μIU/mL/405.

- Optimal insulin sensitivity: < 1
- Early insulin resistance: > 1.9
- Significant insulin resistance: > 2.9

Examples include:

- A woman with a fasting glucose of 94 mg/dL and an insulin level of 5 μIU/mL has a HOMA-IR score of 94 × 4 ÷ 405 = 0.93 (optimal insulin sensitivity);
- A man with a fasting glucose of 100 mg/dL with an insulin level of 10 μIU/mL has a HOMA-IR score of 100 × 10 ÷ 405 = 2.5 (early insulin resistance);
- A woman with a fasting glucose of 110 mg/dL and an insulin level of 15 μIU/mL has a HOMA-IR score of 110 × 15 ÷ 405 = 4.1 (significant insulin resistance).

Beyond insulin resistance and diabetes, other factors that have a major effect on the risk for Alzheimer's disease include: age, a history of depression, a history of a head concussion, and the ApoE4 genotype, which are all associated with an elevated risk for Alzheimer's disease and dementia. (*See Table 1.*)

Other factors to be considered in an assessment for memory loss include detailed neurological examination, hyponatremia, hypothyroidism, vitamin B12 deficiency, hormonal imbalances, sleep apnea, mercury or lead toxicity, hydrocephalus, cerebral vascular disease, and other neurological diseases.

With these risk factors in mind, the most recent paradigm has been to think of Alzheimer's disease as a 20-year progression advancing from no cognitive problems, to subjective cognitive impairment, to mild cognitive impairment, and finally to being disabled with Alzheimer's disease.[12]

The pre-symptomatic phase (no symptoms) lasts about five years. During this phase, a patient's memory might be worsening, but he or she has not noticed that memory loss is a problem.

The subjective cognitive impairment phase occurs next, and patients are more forgetful. Although their family and friends may notice that they keep forgetting things, they are not impaired, and they can still live in their home and work at their job. This phase typically worsens over 10 years.

Without a dramatic change in lifestyle, a patient with subjective cognitive impairment likely will advance to mild cognitive impairment, which is the last step before Alzheimer's disease. Mild cognitive impairment does not mean just mild symptoms, but more specifically, mildly disabled. At this stage, patients are more than absentminded, as now they are impaired. If they work, they no longer may be capable of doing

Table 1. Risk Factors for Alzheimer's Disease

Condition	Risk Increase Compared to Healthy Adults
Age	At age 65 years, 7-10% of people have dementia At ≥ 65 years, 13% have Alzheimer's At age 80 years, 17-25% have Alzheimer's At ≥ 85 years, 40% have Alzheimer's
Elevated fasting glucose (≥100 mg/dL)	Up to a 60% greater risk (which is now 30% of the adult population and 50% of baby boomers)
Diabetes, not using insulin therapy	300% greater risk for Alzheimer's
Diabetes, using insulin therapy	400% greater risk for Alzheimer's
Hypertension (> than 140/90 mmHg)	24% at midlife, up to 300%; increased risk late in life
Tobacco use	50% greater risk for Alzheimer's
Obesity	70-100% greater risk
History of depression	Increases risk for dementia 200% in women Increases risk for dementia 400% in men
Severe head injury	450% increased risk for dementia
ApoE4 genotype	1 of 2 alleles increases the risk for Alzheimer's disease threefold (300%) 2 of 2 alleles increases the risk for Alzheimer's disease 15-fold (1,500% increase)

their job well. Although they may be able to live at home, it may be a real challenge to pay bills and be safe. On average, mild cognitive impairment worsens over the next five years.

Finally, the progression from mild cognitive impairment to Alzheimer's disease occurs at a rate of 10-15% per year,[13,14] depending on the risk factors and the population studies. At this point, the patient is disabled and likely is no longer able to live on his or her own. The patient becomes dependent on caregivers.

There are several types of dementia, many of which overlap (such as Alzheimer's and vascular dementia, caused by stroke or insufficient blood flow to the brain). Approximately 60-70% of dementias are related to Alzheimer's disease, 15-25% to vascular dementia (which tends to occur in a step-wise fashion following mini-stroke after mini-stroke, instead of a gradual decline), plus other less common forms, such as frontal temporal dementia, Lewy body dementia, and dementias related to other neurological diseases, such as Parkinson's disease, Huntington's disease, and Creutzfeldt-Jakob disease. Some of the types of dementia, such as Alzheimer's and vascular dementia, also overlap.

Cognitive Testing

For patients with symptoms of cognitive dysfunction and/or memory loss or at high risk and wanting testing, objective cognitive testing can help to clarify a patient's status. The most common test is the Mini-Mental State Examination (MMSE), a 30-point questionnaire used extensively in clinics and hospital settings. Advantages of this widely used tool are that it has been validated in many settings, nearly everyone in healthcare understands the scoring system, it only takes about five to 10 minutes to perform, and it does not require special equipment.

The primary function of the MMSE is to screen for dementia, which can be a disadvantage for some people. The test is not designed to distinguish between being mentally sharp or dull, and it likely will not identify the very first signs of cognitive loss. Sample questions include:

- "What is the year? Season? Date? Day? Month?"
- "Where are we now? State? County? Town/city? Hospital? Floor?"
- "Count backward from 100 by sevens." (93, 86, 79, 72, 65, …)
- "Repeat the phrase: 'No ifs, ands, or buts.'"

For a full list of the questions, see the appendix and figure at http://www.dementiatoday.com/wp-content/uploads/2012/06/MiniMentalStateExamination.pdf. This test is most useful for screening for dementia. By the time some patients take (and sadly fail) this test, they often are mentally disabled and have become dependent on others for care. Using a 30-point scale, normal generally is considered a score > 27. Depending on the patient's education, many scientists would consider a MMSE score of 26-27 as mild cognitive impairment and a score below 23-25 as dementia.

Another concern with using the MMSE is that if a person is hearing-impaired, for instance, or has another physical disability, it is possible that he or she will score low on the MMSE, although his or her cognitive function may be healthy. The MMSE is not designed to account for such variables and is only a guide for dementia diagnosis. It must be combined with clinical savvy, and healthcare professionals should not make a diagnosis of dementia based solely on the MMSE. Although it is widely administered in the health field, it is not designed to clarify a person's baseline cognitive function and/or mental sharpness, especially not for high-functioning patients.

In addition to verbal cognitive testing, other tools are available to assess cognitive function using a

computerized neurocognitive battery. The Central Nervous System Vital Signs (CNS VS) is a computerized tool to assess memory, brain speed, attention, and executive function. The CNS VS takes about 30 minutes to perform and can be used every one to two years to monitor cognitive function over time. The aim is to identify a drop in cognitive performance 10-15 years before someone has significant memory loss, to allow time to try various interventions that may prevent that decline. Computerized cognitive testing requires a quiet, non-distracting testing area, the patient's ability to follow on-screen instructions, and access to a medical assistant or technician to provide setup and initial training for the patient. The CNS VS test is associated with a modest fee to the company, but computerized neurocognitive testing is supported widely by Medicare and commercial insurances, with excellent reimbursement with appropriate medical necessity.

The CNS VS7 is a computerized neurocognitive test battery comprised of seven familiar neuropsychological tests that generate independent scores; the test scores comprise cognitive domains. The final neurocognitive index score is then calculated as an average of the four domain scores.

The first factor is complex information processing (CIP), commonly referred to as executive function, which is comprised of three tests: 1) Symbol digit coding, based on the symbol digit modalities test;[15] 2) The Stroop test,[16] which has three parts that generate simple and complex reaction times (averaging the two complex reaction time scores generates the "response time" score); and 3) The Shifting Attention test to measure the subject's ability to shift from one instruction set to another quickly and accurately.[17,18] The second factor is effortful attention, comprised of two tests: the number of errors committed during the Stroop test, and a conventional continuous performance test (CPT). The CPT is a measure of vigilance or sustained attention.[19] The third factor is memory with verbal memory and visual memory components.[20] Fifteen words and 15 shapes are provided initially. After one minute and after 30 minutes, the subject is asked to select the original 15 words and shapes from a total of 30 words and shapes. The fourth factor is motor speed, calculated from the finger tapping test and the simple reaction time test in the Stroop test. The choice reaction time score is from the CPT.

Scores are standardized by adjusting for age (on the basis of data from 4,400 normal subjects 6 to 96 years of age) to a mean of 100, with a standard deviation of 15. Test-retest reliability and concurrent validity of the VS7 battery are comparable to similar conventional neuropsychological tests.[21] The discriminant validity of VS7 has been established in studies of patients with mild cognitive impairment and early dementia,[22] post-concussion syndrome and severe traumatic brain injury,[23] attention-deficit/hyperactivity disorder,[24,25] depression,[26,27] and schizophrenia and bipolar disorder.[28]

Published Studies

Various randomized, clinical trials and observational studies have examined how lifestyle factors affect cognitive performance. Efficacy of lifestyle changes in modifying practical markers of wellness and aging was a 10-week, randomized control study conducted in a wellness center in St. Petersburg, Florida.[29] Participants were adults 21 to 65 years of age who exercised on average one day per week or less. Fifty-six subjects were randomized to a control or an intervention group. Subjects followed a diet with many similarities to a Mediterranean diet, and were taught in a weekly exercise session by a trainer to exercise aerobically five to six days per week and to perform strength training two to three days per week. Subjects also were asked to participate in 10 minutes of stress management activities daily.

The study was designed to determine changes in body composition, fitness, and cognition using CNS VS testing. Half of the intervention group followed recommended lifestyle changes and half only made partial improvements. When the entire intervention group was compared with the control group, improvements in body composition, weight, cholesterol profile, and fitness were noted, but the 10% improvement in cognitive function was not significant. However, when the 50% of subjects who followed the program were analyzed separately, there was a significant 24.6% improvement in cognitive flexibility (a measure of executive function). The control group did not show any significant changes. These findings suggest that a Mediterranean-style diet high in fiber (featuring vegetables, fruits, beans, and nuts), combined with activity and stress management, can improve several markers of wellness and aging, including cognitive function.

To assess the effect of physical activity on cognitive function, another study included 91 healthy adults from a wellness center. Over a 10-week intervention, controls were aerobically active zero to two days per week. Half of the members of the intervention group were active three to four days per week and half of them were active five to seven days per week. Neurocognitive data were analyzed by repeated measures comparing minimal aerobic exercise (the control group) to moderate aerobic exercise (three to four days per week) and to high aerobic exercise (five to seven days per week).

Over a 10-week period, increasing frequency of aerobic activity was associated with enhanced cognitive performance, in particular cognitive flexibility, a measure of executive function. Subjects in the control group showed no significant improvement, those with moderate aerobic activity showed a 5% improvement, and those with more vigorous exercise five to six days per week showed a 32% enhancement in cognitive flexibility. These findings are consistent with other clinical studies that have shown less cognitive decline and improved frontal lobe cognitive activities in subjects with higher physical activity levels.[30,31,32]

Another study analyzed a database to clarify the role of long-chain omega-3 intake from fish and fish oil consumption, as well as mercury levels from eating seafood.[33] Although eating fish is associated with methylmercury intake, the cognitive neurotoxicity of mercury is thought to be outweighed by the beneficial effects of a diet rich in long-chain omega-3 fatty acids (N3FA). The objective of this study was to clarify the effect of mercury and seafood intake on cognition. This was a prospective, cross-sectional analysis of 384 men and women attending an all-day comprehensive physical evaluation. At their initial evaluation, researchers measured body composition, cardiovascular status, fitness, diet (including specific types of seafood intake), and laboratory measures (including whole blood mercury). Each subject was tested with CNS VS. Patients with high mercury levels performed 4-5% lower in tests of complex information processing, and patients with normal mercury levels performed 2% lower, compared to patients with mercury levels in the 5-15 mcg/L range.

An increase in N3FA intake from food or supplements was associated with a linear improvement in complex information processing. There was a direct, linear relationship between N3FA intake and blood mercury levels, and the interaction of mercury and N3FA intake accounted for the relationship between mercury levels and cognition. Excessive seafood intake, particularly large-mouth fish species (tuna, grouper, snapper, bass, swordfish), elevated mercury levels and caused cognitive dysfunction, especially at a mercury level ≥ 15 mcg/L. Initially, higher N3FA intake was associated with improved cognitive function, yet N3FA intake exercises a moderating effect that ultimately is overwhelmed by rising mercury levels.

A prospective, cross-sectional analysis of 536 men and women attending an executive evaluation program assessed how cardiovascular risk factors affect cognitive function scores.[34] Researchers measured body composition, cardiovascular status, fitness and diet, and laboratory measures, including carotid intimal media thickness (carotid IMT). Each subject was tested with a computerized neurocognitive test battery. CIP is independently related to carotid IMT scores ($P < 0.01$) as are other cardiovascular biomarkers, including aerobic capacity and dietary intake of fiber, vitamin B12, and N3FA ($P < 0.01$ for each). The findings support other studies that show a relationship between cardiovascular risk factors and cognitive function.

As rates of mild cognitive impairment and Alzheimer's disease are increasing rapidly, and none of the current treatment regimens are effective in arresting progression, it is critical to clarify which lifestyle factors best predict cognitive function. A prospective cross-sectional analysis was conducted of 799 men and women undergoing health and cognitive testing every one to three years at an outpatient center.[35] This study used data collected from the first patient visit. Participants were 18 to 88 (mean = 50.7) years of age and the sample was 26.6% female and 73.4% male. Measurements were made of body composition, fasting laboratory and anthropometric measures, strength and aerobic fitness, nutrient and dietary intake, and carotid IMT. Each participant was tested with a computerized neurocognitive test battery. Cognitive outcomes were assessed in bivariate analyses using t-tests and correlation coefficients and in multivariable analysis (controlling for age) using multiple linear regression.

The initial bivariate analyses showed better neurocognitive index (NCI) scores with lower age, greater fitness scores (push-up strength, VO_{2max}, and exercise duration during treadmill testing), and lower fasting glucose levels. Better cognitive flexibility scores also were noted with younger age, lower systolic blood pressure, lower body fat, lower carotid IMT scores, greater fitness, and higher alcohol intake.

After controlling for age, factors that remained associated with better NCI scores included no tobacco use, lower fasting glucose levels, and better fitness (aerobic and strength). Higher cognitive flexibility scores remained associated with greater aerobic and strength fitness, lower body fat, and moderate intake of alcohol. Modifiable biomarkers that affected cognitive performance favorably include greater aerobic fitness and strength, lower blood sugar levels, moderate alcohol intake, lower body fat, and avoidance of tobacco. Further studies are warranted to study whether modifying these lifestyle factors improves cognitive function and slows cognitive decline.

Treatment Strategies to Improve Cognitive Function and Prevent Memory Loss

Although the strongest potential to prevent memory loss and cognitive decline appears to be associated with preventing and/or reversing insulin resistance and diabetes, other factors, such as exercise, toxins, and cardiovascular risk factors, also are associated with the risk for memory loss and cognitive decline.

One of the challenges with cognitive decline is that often it is not just one to two risk factors that might be involved, but rather 10 to 20 risk factors for memory loss may be present at the same time. Patients have lab abnormalities, such as high blood sugar, multiple nutrient deficiencies, inactivity, hormone imbalances, gut issues, inflammation, and toxin exposures. Ideally, the same program could address all those issues.

Scientists generally like to study one action at a time, such as a trial of fish oil supplements or a specific exercise routine, to gauge its effectiveness. The risk of losing memory is related to multiple factors, which include insulin sensitivity, nutrient deficiencies, a history of brain trauma, obesity, hypertension, smoking, diabetes, depression, poor sleep, and elevated cholesterol levels. Likewise, the ability to decrease these risk factors and avoid dementia rests upon multiple approaches, and

for maximum benefit, preferably all at once. Focusing on a sole aspect likely will not be as effective as treating the whole person.

Scientific articles that reviewed single interventions — from adding a daily workout to adding a particular supplement — to treat dementia generally come to the same conclusion: Stand-alone strategies, such as adding vitamin B12, engaging in vigorous exercise, lowering mercury levels, or other interventions, often showed mixed results, with some studies showing more benefits and others none. Anyone in search of a single effective treatment for memory loss might find this field of research to be confusing, frustrating, and inconclusive.

However, when intervention trials use multiple treatments simultaneously, the outcomes are quite different. Such trials consistently show dramatic improvements in brain function and a decrease in cognitive decline. The FINGER study,[36] conducted from 2009-2011, followed more than 2,600 individuals between 60 to 77 years of age, who had risk factors for heart disease and/or signs of early cognitive decline. In this randomized, clinical trial, which took place during a two-year period, half were in a control group (given general health advice, but no prescribed changes to their lifestyle), and half were assigned to a combination intervention featuring a Mediterranean-style diet (plant-based meals flavored with fresh herbs and spices; healthy fats like olive oil, nuts, and seeds; smaller portions of animal protein), exercise, cognitive training, and cardiovascular disease risk reduction.

Those in the multi-therapy intervention group showed improved baseline scores on overall cognitive function, and cognitive decline was slowed. Also, the dropout rate was low, despite the initial concern among researchers. Combining different types of interventions seemed to improve compliance, perhaps because the subjects making these changes consistently felt better and were motivated to stick with it.

The nonprofit Alzheimer's Association, a global organization dedicated to Alzheimer's prevention, care, and research, has looked at the latest studies and science that feature multiple interventions, such as regular physical activity combined with the prevention/management of diabetes and obesity and cognitive training. It concluded that a varied approach shows the most promise in reducing the risk of dementia and improving brain function. It also endorses food choices that are heart-healthy and beneficial to the brain and advocate following a Mediterranean diet.

First, Stop Insulin Resistance by Eating Foods With a Low Glycemic Load

To address the number one cause for cognitive dysfunction and memory loss — and abnormal blood sugar regulation — it is important to improve insulin sensitivity and stop insulin resistance. The easiest way to improve insulin sensitivity is to choose foods with a low sugar load, also known as a low glycemic load. Glycemic load refers to how high blood sugar levels rise after a serving of food ("glyc" = sugar, and "emia" = blood level). Glycemic load is divided into three categories: low glycemic load refers to foods with a score ranging from 0 to < 10, medium is scores from 10 to < 20, and high is scores > 20.

If a patient has insulin resistance, something as simple as breakfast can have a negative effect on cognitive function. In a study assessing food intake and cognitive function in middle-aged, overweight women with insulin resistance, eating a low glycemic load breakfast has been shown to improve cognitive function.[37] The contrary is also true: Eating a high glycemic load breakfast (pancakes, toast, cereal, bagels, pastries, orange juice) can worsen cognition.

The glycemic index concept became quite popular in the dieting community after it was first introduced, since some saw it as a way to simplify and speed weight loss. The diet mantra was to avoid the high glycemic index foods (because they were packed with sugar). People were encouraged to choose low glycemic index foods, with the hope that the pounds would fall away. Some food companies even label products as low glycemic index to attract diet-watchers.

Unfortunately, the glycemic index concept is not that simple. Alhough the index can be useful when it is interpreted properly, it is not the best decision-making tool, in part because it is impractical in the real world and it is easy to misuse. For example, on the index, pasta is rated a moderate glycemic index food but carrots are high. Therefore, the average person might think that pasta is a healthier (less sugary) choice than carrots.

The index was developed largely as a research tool by Dr. Jennie Brand Miller, a scientist at the University of Sydney in Australia, who has done extensive research on how food affects blood sugar levels, to help assess how foods affected blood sugar control. Typically, researchers measure blood sugar levels after an individual consumes 50 grams of carbohydrates from a single food. This equates to about 1 cup of cooked pasta, which for most people would be a pretty small portion.

By contrast, to get 50 grams of carbs from carrots, one would have to eat nearly nine large carrots in one sitting, which is not realistic. Nutrient-dense carrots are healthy, and like most vegetables, have a very low effect on blood sugar levels. Avoiding them because they appear on the high part of the glycemic index is a mistake, as carrots have a glycemic load of 4, which is low. Beets are another food with a high glycemic index but have a low glycemic load; their sugar effect per serving is very low.

As it turns out, adding more fiber, especially from beans, is an effective way to improve glycemic control. The irony is that some people, including those who follow a Paleo diet, avoid beans because they are high on the glycemic index scale, but beans do not behave the way sugar does in the body.

Table 2. Glycemic Load in Various Foods

Food Source	Low Glycemic Load	Medium Glycemic Load	High Glycemic Load
Fruit	Berries, cherries, pineapple, grapes, watermelon, kiwi	Banana, dried fruit	
Vegetables	Kale, broccoli, carrots, beets, peas, peppers, avocado	Sweet potato	Baked potato, mashed potato, potato chips
Grains	Steel cut oatmeal	Rolled oats, quinoa, whole grain pasta, corn tortillas, wild rice	White bread, whole wheat bread, flour tortillas, crackers, granola, instant oatmeal, brown rice, white rice, corn
Legumes	Black, kidney, garbanzo, lentils, cannellini, navy beans	Baked beans (canned with sauce)	
Animal Protein	Eggs, meat, poultry, fish	Plain yogurt	Yogurt (fruit flavored)
Snacks	Guacamole, dark chocolate, hummus	Popcorn	Tortilla chips, pretzels
Nuts	Almonds, pecans, walnuts, pistachios, hazelnuts, macadamia nuts, peanuts, pine nuts		

A brief selection of low, medium, and high glycemic load foods is listed in Table 2. For an extensive list of foods, see the glycemic index and glycemic load food list at the University of Sydney site: www.glycemicindex.com.

Second, Follow a Mediterranean Diet

The heart-healthy benefits of the Mediterranean diet — famous for its generous use of olive oil, Mediterranean herbs and spices, and red wine, and for the longevity of its adherents — are well documented. What is fairly new is the evidence that it offers impressive cognitive benefits as well. The overall diet is rich in plant foods and light on animal protein, and is characterized by an abundance of bioactive phytonutrients, beneficial plant compounds, with antioxidant and anti-inflammatory properties.

A typical daily Mediterranean diet includes five servings of vegetables, two to three servings of fruit, one to two servings of beans, five servings of fat (nuts, olive oil, seeds), one to two servings of fermented foods (such as yogurt and raw-milk cheese), an abundance of herbs and spices, and one to two servings of whole grains. It also includes seafood three to four times per week, poultry two to three times per week, and red meat typically less than once per week. Followers drink water, coffee, tea, and red wine. In recent times, they have added cocoa and dark chocolate.

Many studies have linked the Mediterranean diet to overall longevity, but its effect on the brain is particularly striking.[38,39] In one study of healthy elderly people (the average age was 80 years and the subjects showed no signs of dementia), researchers analyzed diet and brain size. They discovered that individuals who ate more fish and less meat — consistent with the Mediterranean diet — had higher brain volume, a significant finding suggesting that memory loss and dementia are linked to brain shrinkage.[40]

The acclaimed Mediterranean Diet study from Spain, (The PREDIMED study[41]) is considered one of the most conclusive studies comparing the health benefits of a standard low-fat diet to a Mediterranean diet with liberal amounts of olive oil and nuts. The study showed that people in the low-fat diet group developed higher rates of cognitive impairment and dementia than the olive oil and nut group. Those who ate more olive oil and nuts had better cognitive scores than the low-fat eaters.

A hallmark of the traditional Mediterranean diet is not just what foods are eaten and how much fat is consumed, but it is also a leisurely, pleasurable way of eating with friends and family, with fresh foods that are local and seasonal. Meals are heavily plant-based, with animal protein served in small portions or as a condiment, and vegetarian dishes drizzled with olive oil and herbs playing a major role at the table. The diet comes with an active lifestyle that is much more robust than that of most Americans. After all, this was the diet of farmers, fishermen, olive growers, shepherds, laborers, and people who worked the land and sea. In many ways, the Mediterranean diet and its associated lifestyle is a multifaceted intervention with food, nutrients, activity, and stress management all combined together to be maximally effective.

Third, Consume Specific Foods

Beyond selecting foods with a low glycemic load and avoiding or limiting foods with a high glycemic load, there are two groups of foods that clearly have been shown to help improve

cognitive function or to help slow cognitive decline:

- Flavonoid-rich foods (green leafy vegetables, nitrate-rich vegetables, berries, cocoa and dark chocolate, coffee and tea, and red wine);
- Smart fats (olive oil, nuts, seafood).

Flavonoid-rich Foods. Green leafy vegetables are rich in flavonoids but also are packed with fiber, folate, and antioxidants. They decrease inflammation body-wide, and since they provide fiber with minimal glycemic load, eating them improves blood sugar control. Good options include foods like kale, broccoli, spinach, and other greens. Studies have shown that those who consume one cup of green leafy vegetables daily have slower cognitive decline and higher cognitive scores than those who do not consume green leafy vegetables.[42,43] In evaluating a variety of foods, green leafy vegetable intake provided the greatest protection.

Beyond leafy greens, vegetables rich in nitrates improve blood pressure and increase blood flow to the part of your brain that enhances cognitive performance.[44,45] By far, beets, which also have a low glycemic load, are the best source of brain-enhancing nitrates, but other options are arugula (also called rocket salad), spinach, and dark green lettuce.

Blueberries have been shown to improve cognition and slow cognitive decline, and also to reduce the production of beta-amyloid, the protein associated with Alzheimer's disease.[46,47,48] Ideally, people should aim to consume at least one cup of blueberries or other berries or cherries for their dark blue, red, and purple flavonoid pigments daily.

Another popular and delicious source of flavonoid pigments is dark chocolate and cocoa. With functional MRI brain imaging, researchers have shown that consuming cocoa improves cerebral blood flow to the memory center of the brain, the hippocampus.[49] More recent research has shown that drinking cocoa every day for eight weeks improved cognitive testing results in older adults, especially for those with early cognitive decline.[50] For the best cognitive benefit, look for cocoa brands labeled "non-alkalized" to ensure maximum flavonoid content. When it comes to selecting dark chocolate for brain benefits, do not confuse milk chocolate with dark chocolate. It must be at least 74-80% cacao to have proven benefit.

The most common source for flavonoids in the American diet doesn't come from food, but rather a beverage — coffee. Although most studies have shown that coffee is good for the brain, there has been some debate about the ideal amount, and whether the benefit is from caffeine or the flavonoid pigments in the coffee. More recently, researchers analyzed more than 34,000 subjects and found that people who drank one to two cups per day showed the lowest risk for memory loss. This was better than those who drank no coffee or those who drank more.[51] Similarly in Japan, a study with more than 23,000 adults 65 years of age or older showed a 20-30% reduction in advanced dementia in those who consumed two to four cups of coffee daily.[52] Even decaffeinated coffee has been shown to improve cognitive function in men and women.[53]

As promising as the science linking coffee with brain benefits is, tea consumption looks even better. Worldwide, tea offers one of the largest sources for daily flavonoid intake. Yet, tea provides flavonoids, caffeine, and something more, L-theanine, an amino acid that helps cognition. In one study, researchers combined 97 mg of L-theanine and 40 mg of caffeine in a single tablet for one group of subjects and compared it to a placebo given to another group. Those who took the combination showed a significant improvement in cognitive accuracy during task switching, an improvement in alertness, and less self-reported fatigue.[54] Tea drinkers consistently show less cognitive decline than non-tea drinkers, and women appear to have more cognitive benefit from drinking tea and coffee than men.[55,56]

Red wine is another common source for flavonoid intake. For many years, moderate red wine intake has been associated with cardiovascular benefits, but more recently it has shown cognitive benefits as well. Beer and hard liquor consumption have not shown the same cognitive benefits. In a study in New York City, residents over 65 who drank wine (but not beer or liquor) had larger brain volumes, indicating less brain shrinkage, than those who did not drink wine. In this study, consumption clearly was moderate, as women averaged one serving per day and men had one to two servings.

Regardless of whether they had the Alzheimer's-related ApoE4 gene, they showed the same benefit.[57] A study in the Netherlands tracked people aged 43 to 70 years over five years. Those who drank two to three servings of red wine per day showed less cognitive loss than those who abstained or those who drank more than three servings per day.[58] In France, researchers assessed alcohol intake in 3,088 middle-aged adults and measured their cognitive function 13 years later. Women who consumed one to two servings of wine daily and men who had two to three servings daily had better cognitive function than those who had none or who had it infrequently. Again, heavy drinking showed worse cognitive function.[59]

So, like coffee and tea, red wine in moderation, not in excess, is good for cognitive function and helps prevent memory loss. However, not everyone can drink alcohol in moderation, so if someone avoids alcohol intake, they may have good reason for doing so.

Smart Fats

As discussed previously, there is strong evidence that consuming one to two tablespoons of extra virgin olive oil per day improves cognitive function and appears to slow cognitive decline. In the same Mediterranean diet study conducted in Spain, consuming one to two ounces of nuts also

was shown to enhance cognitive scores and reduce cognitive decline. Not all fats, but certain fats appear beneficial and essential for the brain.

Another source of essential, smart fats for the brain are long-chain omega-3 fats. Consuming more of these long-chain omega-3 fats is associated with better brain processing speed and greater executive function. The best benefit occurred in those consuming two to three servings per week of cold water, small mouth (low mercury) fish, such as wild salmon, sardines, sole, oysters, and mussels. Epidemiological studies consistently have shown a lower rate of Alzheimer's disease in those who consume more long-chain omega-3 fats.[60] In clinical studies, both adults and children experience cognitive benefits from consuming long-chain omega-3s. The lower the blood level of these long-chain omega-3 fats to start, the greater the benefit from consuming them — and children appear to benefit more from consuming omega-3 fats than adults.[61] However, as promising as these long-chain omega-3 rich fats are for long-term brain health, studies using long-chain omega-3 fats alone have not shown consistently that they can reverse advanced cognitive impairment.

Improve Aerobic Fitness and Strength Training

Beyond food, studies show that being physically active is also essential for a healthy brain. Exercise increases blood flow to the brain,[62] and it helps to improve insulin sensitivity and restore normal blood sugar regulation. Both aerobic fitness and strength training independently help to improve processing speed and overall executive function,[63] and daily vigorous aerobic activity has more benefit than moderate activity three days per week.

Several studies have shown that intense aerobic exercise training improves blood sugar control and enhances insulin sensitivity.[64, 65] A study in the United Kingdom assigned 90 inactive subjects to either daily moderate aerobic activity or interval training.[66] Those in the interval training group exercised for 20 minutes three times per week (about one hour total per week). Those in the moderate aerobic group worked out 125 minutes per week (more than two hours), spread across five days. The results showed both groups had the same reduction in insulin resistance. Thus, another potential advantage of more intense training is to gain the same benefits in half the time.

Maintaining muscle mass has been shown to help prevent brain volume shrinkage over time, and regular strength training has been shown to increase the size of the hippocampus even in patients 80 years of age.[67] In a study in Australia, men and women 55 years of age or older were assigned randomly to groups for cognitive training through a computer program or for strength training two to three days per week. Those in the computer-based cognitive training group showed modest improvements in memory, but only those in the strength training group showed significant improvements in cognitive function and memory.[68]

In addition, being aerobically fit improves brain processing speed and executive performance, but of interest, the time spent exercising each week does not predict any benefit in cognitive function — what counts is the fitness level achieved. Being physically fit has been shown to result in larger brain volumes in children and in adults, so the benefits are true for any age.[69]

Summary

The prevalence of cognitive decline and dementia is increasing at rapid rates and poses serious challenges for our health system. Although current medication therapies that can stop the progression of cognitive decline are lacking, there is evidence that lifestyle changes can improve cognitive function and prevent and/or slow cognitive decline.

The largest preventable cause for cognitive decline appears to be insulin resistance and abnormal blood sugar control, both of which can be reversed with appropriate lifestyle interventions. A brief sample of effective lifestyle interventions that improve insulin sensitivity and cognitive function include eating low glycemic load foods, adopting a Mediterranean diet, adding specific foods that have been shown to slow cognitive decline, and adding both aerobic activity and strength training with the aim to improve fitness.

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CME Questions

1. Which of the following does *not* increase the risk for cognitive decline?
   a. Insulin resistance
   b. Inactivity
   c. Elevated total and LDL cholesterol levels
   d. Low vitamin D levels

2. Which food has a high glycemic load?
   a. Steel cut oats
   b. Whole wheat bread
   c. Broccoli
   d. Sweet potato

3. Which factor improves insulin sensitivity?
   a. Eating low glycemic food instead of high glycemic food choices
   b. Interval training
   c. Weight lifting
   d. All of the above

4. Which activity is *not* associated with better brain processing speed?
   a. Strength training
   b. Aerobic activity
   c. Consuming more extra virgin olive oil or nuts
   d. All of the above are associated with better brain processing speed

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