

WORKSHOP
REPORT

Achieving & Maintaining Cognitive Vitality with Aging

ACHIEVING AND MAINTAINING COGNITIVE VITALITY WITH AGING



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INSTITUTE FOR THE STUDY OF AGING

The Institute for the Study of Aging, Inc., is a private, nonprofit foundation based in New York City. The Institute is one of the largest private sources of philanthropic funding for drug discovery and drug development in cognitive aging and Alzheimer's disease in the United States and internationally.

The mission of the Institute is to promote quality of life in old age. As cognitive impairment is the most significant threat to successful aging, the Institute's primary focus is to facilitate and promote the discovery and development of new therapies to treat the aging-related problems of cognitive decline and, specifically, Alzheimer's disease. Through the sponsorship of research conferences and workshops, the Institute is dedicated to finding ways to promote "cognitive vitality" with aging.

INTERNATIONAL LONGEVITY CENTER—USA

The International Longevity Center—USA is a not-for-profit, nonpartisan research, policy, and education organization whose mission is to help societies address the issues of population aging and longevity in positive and constructive ways and to highlight older people's productivity and contributions to their families and society as a whole.

The organization is part of a multinational research, policy, and education consortium with centers in the United States, Japan, Great Britain, France, and the Dominican Republic. These centers work both autonomously and collaboratively to study the impact of increased life expectancy and higher proportions of older people on nations around the world.

CANYON RANCH HEALTH RESORT

Canyon Ranch Health Resort, located in Tucson, Arizona and Lenox, Massachusetts sponsors workshops on nutrition, fitness, health, and longevity as part of a comprehensive approach to wellness. The resort offers a wide array of services provided by nutrition, fitness, medical, behavioral, and spiritual experts.

NATIONAL INSTITUTE ON AGING

In 1974, Congress established the National Institute on Aging (NIA), whose mission is to provide leadership in aging research, training, health information dissemination, and other programs relevant to aging and the elderly and, in doing so, to improve the health and well-being of older Americans. As one of the 25 institutes and centers of the National Institutes of Health, the NIA leads a broad scientific effort to understand the nature of aging and to extend the healthy, active years of life.

The ideas, conclusions, and recommendations herein are solely those of the authors, the International Longevity Center, and the Institute for the Study of Aging and not those of the National Institute on Aging.

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Preface

Perhaps the greatest fear of old age is losing one's mind. Cognitive function affects a person's ability to interact and enjoy life. Loss of the mind may translate into an inability to even recognize one's loved ones. Fortunately, the results of recent clinical work and research insights are increasing our ability to influence mental health status in aging.

The "longevity revolution" has increased our focus on many aspects of health in aging, including cognitive health. Cognitive vitality in old age has become an increasingly important health care goal. Although many older individuals are enjoying optimal aging, a substantial number of them still face their later years with serious decrements in cognitive function. These decrements can significantly affect quality of life.¹ And when cognitive decline progresses to dementia, the problem becomes far more serious. Alzheimer's disease (AD), the most common cause of dementia, has a devastating impact on individuals and society.

Our focus on achieving cognitive vitality is a relatively new conceptual approach made possible by new knowledge gained during the past decades from research on cognitive aging and AD. Now, we more clearly understand the distinctions between normal cognitive aging and diseases of cognition in old age. Research has

also resulted in many new preventive and therapeutic strategies for AD, and the possibility of new therapies and lifestyle interventions allows us to imagine that cognitive vitality in old age is an achievable goal. Now, we understand enough about risk factors for dementia to begin to design, test, and implement preventive strategies in clinical practice. This new knowledge makes it possible to begin to focus on the prevention of cognitive decline and the maintenance of cognitive vitality in older persons.

Achieving and maintaining cognitive vitality with (indeed, despite) aging has been a concern we have shared for some years.² Educating the public about the promotion and protection of cognitive health is an important goal. It requires assessment and reduction of risk factors for cognitive decline. This focus on cognitive vitality marks an expansion beyond traditional recommendations of health promotion and disease prevention, as we believe mental and physical health can be maintained and promoted. We want to emphasize that such a program is a lifelong commitment that is based on an awareness of the interactions of mind and body.

We believe this workshop report and its publication on the websites of the International Longevity Center (www.ilcusa.org) and the Institute for the Study of Aging (www.aging-institute.org) will serve the public.

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Executive Summary

6

More people today are living longer lives than ever before, and longevity is already commonplace in both developed and developing countries. Substantial gains in life expectancy and in the number and proportion of older people throughout the world will have a significant impact on our lives and on the programs and policies we design for the 21st century. This longevity revolution represents both an incredible opportunity and a great challenge.

Without doubt, the most prevalent and tragic affliction of old age is mental or cognitive impairment, often resulting in dementia—severe global cognitive impairment.

Cognitive aging is the term used to describe changes in memory and other cognitive functions associated with old age. Most people experience changes in memory and other cognitive functions in old age. In many cases, the cognitive changes associated with normal aging are usually mild and do not impair a person's ability to function on a daily basis. As researchers in the field of cognition, we believe that cognitive aging is potentially avoidable. Our goal is to find ways to maintain cognitive vitality in old age.

Recent studies have begun to classify the different degrees of cognitive impairment associated with aging. The earliest form of age-associated cognitive change, characterized by increased forgetfulness, is called age-associated memory impairment (AAMI). In this stage, subjective complaints of

memory loss are accompanied by objective evidence of impairment. Memory loss associated with AAMI is generally slight. But it may be preventable and treatable.

A more serious form of cognitive impairment with aging is the disorder known as mild cognitive impairment (MCI). MCI is a disorder that can be identified with psychological tests that use learning and memory tasks. Individuals with AAMI do not automatically progress to MCI, but about 15% of individuals diagnosed with MCI do progress to Alzheimer's disease each year.

“Senility” is the lay term for dementia, a syndrome of cognitive impairment that affects all aspects of thinking, including abstract reasoning, judgment, language, memory, and learning. According to US studies, about 25% of people over the age of 75 and about 40% of people over the age of 80 are affected by dementia.

Alzheimer's disease is the most common cause of dementia. As individuals over the age of 85 constitute the most rapidly growing segment of our society, cognitive aging and Alzheimer's disease represent a significant and increasing social and economic burden to individuals, families, and society.

Fortunately, dementia is not an inevitable companion of old age. An alternate scenario—cognitive vitality with aging—is possible. With this in mind, the Institute for the Study of

Aging, Inc., in conjunction with the International Longevity Center—USA, Canyon Ranch Health Resort, and the National Institute on Aging, held an interdisciplinary workshop entitled “Achieving Cognitive Vitality With Aging” at the Canyon Ranch Health Resort in Tucson, Arizona on May 2 - 4, 2000. The workshop brought together expert clinicians and research scientists from diverse backgrounds and areas of expertise to address the issue of maintaining cognitive vitality with aging.

THE AIMS OF THE WORKSHOP WERE TO:

- Review current scientific and clinical knowledge of normal human cognitive aging, the biologic mechanisms that underlie this process, and risk factors associated with mental decline;
- Make recommendations for lifestyle changes to maintain cognitive vitality and prevent mental decline, based on a combination of current scientific and clinical knowledge; and
- Create a research agenda for the development of new therapies to prevent mental decline.

The absence of a complete scientific understanding of the cognitive aging process presented a genuine challenge to the group. While new findings are being published and new technology developed, there remain many secrets about aging. The group strove to identify risk factors for cognitive aging, such as those relating to nutrition, medical conditions, psychological and psychosocial factors, lifestyle, hormones, and genetics. Participants also explored behaviors that may protect against cognitive decline, including learning new things, staying physically active, participating in leisure activities, practicing stress reduction techniques, seeking help for depression, grief, or loneliness, eating a nutritionally balanced diet, stopping smoking, reducing alcohol consumption, and seeking treatment for medical problems. The group studied data on brain plasticity (adaptivity), memory enhancers,

the effects of exercise on the brain and cognition, and interventions to prevent mental decline in animal models. Potential drugs for preventing mental decline and maintaining cognitive vitality, such as acetylcholinesterase inhibitors, as well as drugs not yet approved for prevention and treatment of cognitive decline, were also discussed.

The purpose of this document is to shed light on the process of cognitive aging and to develop strategies to maintain cognitive vitality. By doing so, we hope to increase awareness of the need for more research on the subject. In addition, we hope to give physicians, policy makers, and the general public the tools to promote cognitive vitality. Our goal is to provide information that will ultimately help all individuals maintain cognitive health throughout the aging process and thereby significantly enhance their overall quality of life.

The Workshop Report

By the year 2050, there will be almost 2 billion people aged 60 years and over in the world. At that point, the population of older persons will be larger than that of children (14 years of age) for the first time in recorded human history.³

This process of global aging is happening rapidly. In 1950, approximately 200 million of the world's population was 60 years of age or older. This part of the population has expanded rapidly, and the projected future expansion is dramatic (Figure 1).⁴

What kind of future can these people look forward to? What kind of cognitive function will accompany them into their later years? Many people approach their later years worried about memory loss, shortened attention span, and incompetence in cognitively complex situations.⁵ Some assume that severe cognitive decline is inevitable. In contrast, others look forward to the years past age 65 as a vital, active

time in their lives. Many postpone retirement. Others choose to travel, volunteer, or begin new careers. To maintain the vitality of their bodies and minds, many follow anti-aging advice of uncertain value that they hear about on television

or read about in magazines and newspapers.

People facing their later years need solid, scientific information on this complex topic—they don't need myths or false hope. The Institute for the Study of Aging, the International Longevity

Center, Canyon Ranch Health Resort, and the National Institute on Aging sponsored this workshop to determine what is known and what questions remain to be answered about cognitive vitality with aging. We hope that our efforts will help people understand how cognition changes with normal aging and disease and that this understanding will enable them to make informed decisions about maintaining their own cognitive health.

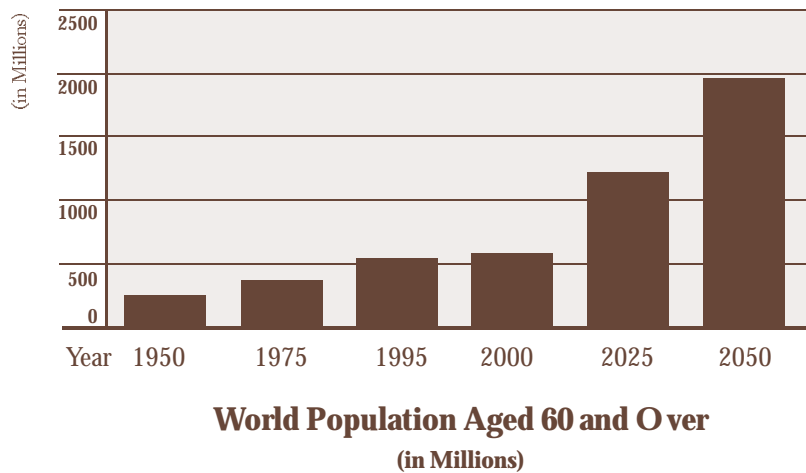


Figure 1. *Global aging: world population aged 60 and over*

WHAT IS COGNITION?

Cognition — The process of knowing. It is a combination of skills, including knowledge acquisition, attention, intuition, memory, language, perception, skilled motor behaviors, decision making, goal setting, planning, and judgment.⁵

Cognitive vitality — Good cognitive function that results from a complex combination of reserve brain capacity, acquired knowledge, and a degree of protection against brain insults. People with high cognitive vitality remain intellectually sharp as they age.^{6,7}

WHY IS COGNITIVE VITALITY IMPORTANT?

Having a clear, active mind at any age is important. For older persons, cognitive vitality may make the difference between dependency and independent living. Even in less dramatic cases, cognitive vitality has a tremendous impact on quality of life.

MAINTENANCE OF COGNITIVE VITALITY HELPS INDIVIDUALS TO ...

- Enjoy everyday life fully
- Be productive (either at work, at home, or through volunteer activities)
- Acquire new knowledge
- Maintain health
- Stay involved
- Maintain independent living
- Maintain social and family relationships
- Be creative
- Face challenges
- Avoid depression

Cognitive function is tightly tied to survival. Studies have shown an association between rapid cognitive decline and increased mortality.⁸ Separating “body” functions from “mind” functions is impossible, and physical health appears to be largely intertwined with mental health and function. After all, the brain is the control center for the body, and much of what we do to maintain our health is a function of “mind over matter.”

THE AGING BRAIN

While we encourage an optimistic approach to cognitive vitality with aging, we cannot ignore that the brain does change with age. As it ages, the rate at which the brain can receive and process information slows. The reasons for this are not well understood. Cognition can be considered a kind of computation process in a network of billions of brain cells. During aging, some links in the network break, resulting in additional time needed to process and react to information. In most cases, a person is not even aware of this change because most common activities do not test the limits of a person’s ability to process information rapidly. However, the bottleneck of slowed processing can cause other shortcomings in cognitive function,⁹ such as the memory lapses that are seen in aging. In addition, complex tasks that require people to access multiple memories simultaneously may be compromised as a person ages.

DID YOU KNOW?

The activity of the brain, like the rest of the body, generally slows down with aging. This is called slowed speed of processing. Loss of function is the key factor in aging. Normally, large numbers of nerve cells are not lost.

Why does the brain “slow down”? One suggestion is that several processes such as those listed below can result in reduced cognitive vitality.

- **Inflammation** — In the brain, inflammatory responses are part of the natural repair process following an injury or infection. However, chronic, uncontrolled inflammation may tip the balance toward brain injury rather than brain repair.¹⁰
- **Oxidative stress** — Metabolic processes produce oxidants (chemicals that damage cells, molecules, and cellular components such as membranes and mitochondria) and antioxidants (chemicals that protect tissues from oxidants). When long-term oxidant activity outweighs long-term antioxidant activity, brain damage occurs.¹¹

Antioxidants — Chemicals such as vitamins C and E that may protect neurons (nerve cells) by decreasing the adverse effects of reactive oxidants and may promote cognitive vitality.

- **Hormonal Changes** — Estrogen acts as a neurotrophin, which means that it protects neurons from damage and promotes the production of new neurons in the brain.¹² Animal studies show that the postmenopausal estrogen decline in women may be one of the factors that accelerate the occurrence of age-related cognitive impairment.¹³

Neurons — Nerve cells, which communicate information in the body. The brain has billions of neurons, which give it a sizable reserve capacity to compensate for neurons that are damaged or destroyed.¹⁴

Neurogenesis — The production of new nerve cells. Recent work indicates that new brain cells can be made even in advanced age.

- **Amyloid deposition** — Beta-amyloid (A β) is the primary protein that comprises the senile plaques that form in the brains of Alzheimer's disease patients. Deposits of this protein in the brain cause brain injury.¹¹

Senile plaques — Deposits of beta-amyloid in the brain that cause brain damage associated with the progressive cognitive decline characteristic of Alzheimer's disease.

Alzheimer's disease — A disease characterized by progressive cognitive decline caused by brain changes such as the degeneration of neurons and the formation of senile plaques and neurofibrillary tangles (abnormal debris inside brain cells).

IS COGNITIVE DECLINE SOMETHING EVERYONE SHOULD EXPECT?

Just as the physical effects of inflammation, oxidative stress, hormonal changes, and amyloid deposition vary from person to person, cognitive functioning varies among people and over time. Mental function generally follows a continuum (*Figure 2*). Some people maintain cognitive vitality as they age, showing only small losses in mental function. While some degree of memory loss can be expected, cognitive or mental decline in some individuals becomes abnormal, beginning a progression that may ultimately end with dementia.¹⁵ The initial stage of this decline may be age-associated memory impairment (AAMI). In this stage, people have subjective complaints and objective evidence of memory loss. Diagnosis of AAMI is difficult. The next stage in the continuum is mild cognitive impairment (MCI), which is marked by even greater memory loss. Specific psychological testing can determine whether the memory loss falls within the normal range or can be

diagnosed as MCI. MCI may progress to dementia. While AAMI and MCI are characterized by memory loss alone, dementia refers to mental decline severe enough to keep a person from functioning normally. It is characterized by memory loss and other cognitive dysfunction (such as impaired abstract thinking). Many people fear dementia. It robs them of their personalities, their ability to interact with others, and their ability to function independently. Alzheimer's disease is the most prevalent cause of dementia in older people.¹⁶

high cognitive function. One study showed that high-functioning older adults smoke less, exercise more, and are more likely to engage in volunteer activities than lower-functioning older adults.²¹ These associations between certain cognitive behaviors and high cognitive functioning are not unexpected. As we shall discuss, people can take behavioral steps to prevent or postpone mental decline.

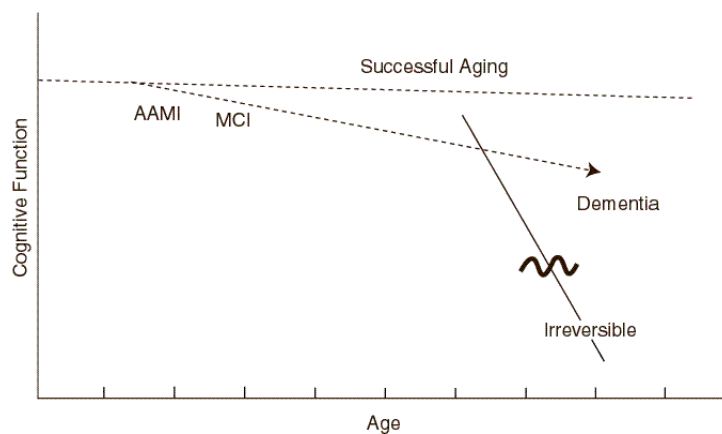


Figure 2. *Model for phases of brain aging*

In this model, some degree of cognitive impairment is associated with “successful aging.” Against this background, abnormal changes can occur that progress through age-associated memory impairment (AAMI) and mild cognitive impairment (MCI) to dementia. At some stage in dementia, irreversible damage apparently occurs. Adapted from Cotman 2000,¹⁰ with permission.

Dementia is not a normal part of aging, as it only affects about 3% to 10% of people over age 65.^{17,19} Also important to note is that not all people diagnosed with MCI will end up with dementia and that long periods may pass before this condition deteriorates into dementia.²⁰ While most people over the age of 70 experience some degree of cognitive decline, particularly short-term memory loss, many people age without any abnormal cognitive decline. Many centenarians (men more than women) maintain

Dementia — A condition marked by progressive cognitive impairment. This condition, by definition, is severe enough to disrupt daily living.¹⁷

Mild cognitive impairment — Perhaps a transitional stage between age-associated memory impairment and dementia, characterized by noticeable memory loss but without other changes in cognitive abilities. Not all people with mild cognitive impairment develop dementia.¹⁸

WHO IS AT RISK FOR COGNITIVE DECLINE?

Certain factors make some of us more likely than others to experience cognitive decline. People need to be aware that some factors cause potentially reversible mental decline and should be addressed by a physician. These include adverse drug reactions, overmedication, depression, metabolic and endocrine (hormonal) disturbance, tumors, trauma, alcoholism, eye and ear problems, and infection.²²⁻²⁴ Other risk factors for dementia, which is not a reversible condition, may be genetic or environmental.²⁵ These factors should be considered in long-term prevention strategies.

Risk factors vary—some can be changed or modified, and some cannot. The following table lists some risks for cognitive decline and/or dementia and categorizes them.

Genetic factors

Female gender²⁶
ApoE4 genotype²⁷

Medical comorbidities

Hypertension²⁸
Heart disease²⁸
Diabetes²⁹
Elevated low-density lipoprotein cholesterol³⁰
High homocysteine levels³¹
Transitory ischemic attacks (TIAs)²⁸
Head trauma³²
Environmental exposure to toxins
(particularly lead)³³

Lifestyle choices

Smoking^{26,28}
Substance abuse, including alcohol and
illicit drugs³⁴⁻³⁹

Psychological/psychosocial factors

Low educational achievement^{26,40-43}
Lack of physical activity⁴⁰
Lack of social interaction/leisure activities⁴⁴
Excessive response to stress
(excessive cortisol levels)⁴⁵

FACTORS/INTERVENTIONS THAT PROMOTE COGNITIVE FUNCTION

Researchers are exploring ways to postpone and/or treat mild dementia. If successful, these therapies may have a broader use and help to keep the mind functioning well as people age. Also, people may be able to reduce the risk of cognitive decline and achieve cognitive vitality by adopting certain preventive strategies that are discussed below.²

LIFELONG LEARNING AND TRAINING

Animal studies have shown that intellectual stimulation actually promotes brain growth.⁴⁶ Studies in people have demonstrated that lower education levels or low language ability in early life are associated with cognitive impairment and dementia in later years.^{41,47} Education has been found to protect against cognitive decline even in those younger than age 65.⁴⁸ Indeed, adult education and educational/intellectual stimulation later in life may help to maintain cognitive health.

Fortunately, the brain maintains its plasticity (adaptivity) even into very old age. In the very old, repeated training can be effective in sustaining higher levels of cognitive performance.⁴⁹ Simply re-testing older subjects during training exercises enhances memory performance.⁵⁰ Training may be formalized or it may consist of doing memory exercises, such as crossword puzzles.

Brain plasticity — The ability of the brain to change in response to stimuli (e.g., learning). Despite myths to the contrary, the brain can rewire itself, even into old age, and some areas of the brain may be able to add new cells in response to stimulation.

EXERCISE

Lack of physical activity has emerged as a risk factor for cognitive decline. Encouraging people to continue engaging in enjoyable physical activities as they age is another way of promoting cognitive vitality. Several studies have shown that exercise has a beneficial effect on the brains of older persons. Active older adults demonstrate improved blood supply to the brain, higher cognitive test scores in some areas, and improved reaction time. Even older adults with physical and emotional impairment benefit from exercise training. As the American workforce ages, employers may find it beneficial to encourage activity and provide exercise opportunities during the workday, as this will help to improve productivity, health, and cognitive function.^{40,51-54}

DID YOU KNOW?

Moderate aerobic activity, like walking, improves function in executive tasks, such as problem solving, in older people who previously had not exercised.⁵⁵

DAILY ACTIVITIES

A rich and stimulating work environment may help maintain cognitive function. This should be an important consideration for a person thinking about retirement.⁵⁶ Social and nonwork activities are also correlated with the risk of cognitive decline in older adults. For this reason, older people should be encouraged to keep working and/or to participate in activities like traveling, knitting, gardening, or volunteering. They should also be encouraged to participate in group activities that provide opportunities for social interaction.⁴⁴

STRESS REDUCTION

Stress reduction techniques have also proved to be important as part of the daily activities of

older individuals. Animal studies have shown that chronic stress alters brain structure and can reduce the body's ability to maintain normal physiologic function, which may, in turn, affect cognitive function.^{57,58}

SLEEP

Older people are often plagued with sleep problems that can negatively affect cognitive function. Controlling sleep disturbances and increasing REM (rapid eye movement or dream) sleep are associated with preserved cognition and function.^{59,60}

EMOTIONAL STABILITY

Studies suggest a connection between cognitive and emotional health. High-functioning older adults report fewer emotional problems and score higher on scales of self-efficacy. Older people who have been married show greater emotional stability and higher cognitive function than their peers who never married.⁶¹ The stress of depression in older adults may actually result in injury to the brain and may be associated with the increase in the rate of suicide among this population, particularly among white men.⁶² Health care professionals and patients, therefore, need to be alert to the symptoms and effects of depression and make sure it is properly treated.^{21,63}

NUTRITION

Nutritional intervention has been investigated as a way to delay and/or prevent cognitive impairment. Some animal studies suggest that reduced caloric intake may protect against the effects of aging. In one study of mice, data showed that a nutritious but restricted calorie diet, introduced at weaning, did not reduce adult brain weight but did reduce adult body size. This study also demonstrated in animals that caloric restriction at midlife does prolong cognitive function, although other data do not support this finding.⁶⁴ At present, doctors do not generally promote dieting in older individuals because it may increase frailty or mask disease-related

weight loss. A balanced diet is vital to preserve general health and vitality.

Researchers are also looking at the role of antioxidants in preserving cognitive vitality and preventing dementia. Antioxidants act as scavengers, protecting the body against free radicals that can damage brain cells.⁶⁵ Free radicals are highly reactive substances that cause damage through chemical processes such as oxidation. Vitamins C and E, along with beta carotene, act as antioxidants. Among people aged 65⁶⁵ and older, those with a higher intake of these antioxidants have better memory performance, suggesting that antioxidants may help prevent progressive cognitive impairment.⁶⁶ Currently, research is under way to investigate whether vitamin E can help prevent or delay Alzheimer's disease in older people with MCI.⁶⁷

Though more research is needed in this area, eating antioxidant-rich fruits and vegetables and/or taking a daily multivitamin may be beneficial. But like all chemical substances, nutrients and other food components can have negative effects if taken in excess. For example, the upper limit of intake for vitamin C for adults over age 50 is 2000 milligrams (mg) a day; more than this can cause renal dysfunction and diarrhea and distort the results of some laboratory tests. The upper limit recommended for vitamin E is 1000 mg a day.⁶⁸

The Institute of Medicine's Food and Nutrition Board recently released the newest dietary reference intake values, which gives suggested daily doses and tolerable upper limits for vitamins C and E. The report does not recommend a daily or upper intake level for carotenoids such as beta carotene, so people should be careful not to take them in high doses. The report recommends taking beta carotene supplements only for the prevention and control of vitamin A deficiency.⁶⁸

THE EFFECT OF MEDICAL PROBLEMS/ INTERVENTIONS ON COGNITION

As people age they often need to cope with medical conditions that may affect cognition. The effects of some conditions, like stroke, may be obvious, while other changes, like hormone levels that are reduced in aging, may affect cognition in more subtle ways.

INJURIES

Brain injuries occur most frequently in two age groups: people aged 15 to 24 years and people aged 75 and older. Brain injury can result in lifelong impairment of physical, cognitive, and psychosocial functioning. Many brain injuries are not treatable, so prevention through precautionary measures such as wearing seat belts, bike helmets, and reflective clothing should be the main focus.⁶⁹ In addition, research has shown that professional soccer players who frequently "head" the ball often suffer from brain injury. With the growing number of children participating in youth soccer programs, parents, children, and coaches should be educated about the potential negative effects of this technique, and it should be discouraged by parents and coaches alike.⁷⁰ Boxing is another sporting activity associated with a risk of brain injury and dementia. In general, people who participate in athletic activities should take caution to ensure that the head is protected.

ALCOHOL AND SMOKING

Some studies have suggested that nicotine may improve information processing and memory.⁷¹ Current research is investigating new drugs that mimic the effect of nicotine on cognitive function.⁷² However, cigarette smoking has numerous long-term adverse effects on the heart, lungs, and brain, and a number of studies show negative effects of smoking on cognition.⁷³

Excessive alcohol consumption can cause nerve cell death, which may contribute to dementia

and is associated with rapid cognitive decline in Alzheimer's disease patients.⁷⁴ Research on people who have Alzheimer's disease, however, excludes people with known heavy alcohol use, leaving many questions about the association of alcohol and Alzheimer's disease unanswered.⁷⁵ Moderate alcohol consumption may help prevent cognitive decline, possibly through effects on the cerebral blood vessels.⁷⁶ But the evidence is not conclusive, and recommending that older individuals use alcohol for medicinal purposes is risky, since alcoholism is a significant problem in this age group.⁷⁷

HORMONAL AND DRUG SUPPLEMENTS

Alzheimer's disease is more common in women than in men, and researchers have found a relationship between estrogen deficiency and Alzheimer's disease. Estrogen may play a role in maintaining neuronal health and some aspects of cognitive function in older women.⁷⁸ Findings suggest that estrogen replacement therapy enhances new learning and helps maintain verbal memory. Results from animal and human studies of estrogen replacement therapy are promising, but the findings are not conclusive.^{12,17,79} Further research is needed to determine whether estrogen replacement therapy can protect women from cognitive decline. Those considering hormone supplements may wish to consider the potential benefit for preventing cognitive decline when assessing the risks and benefits of these therapies. Studies are also ongoing to evaluate the effect of testosterone on cognitive function with aging.

Dehydroepiandrosterone (DHEA), a natural precursor of estrogen and testosterone, has been advertised as a supplement to boost memory and as a cure for many ills of aging. Though DHEA levels do decline as people age, research does not support these health claims.⁸⁰ Until further research is carried out, DHEA is not recommended for the prevention of cognitive decline or for enhancement of cognitive function in older people.

Melatonin, a hormone produced by the pineal gland in the brain, is a highly advertised over-the-counter substance purported to improve the quality of sleep. Some studies show that melatonin levels fall with age, but others do not. Some scientists think that lower melatonin levels may be associated with sleep disorders in some older people, which may in turn cause cognitive impairment. However, until well-controlled clinical trials are conducted, melatonin is not recommended as a long-term supplement.¹⁹

Human growth hormone levels also decline as we age.⁸¹ Half of all people age 70 and older have some deficiency of this hormone. Studies investigating whether human growth hormone can improve cognitive functioning have had mixed results. More studies are needed before treatment with this hormone can be recommended for maintaining cognitive vitality,¹⁹ especially since the long-term adverse effects of this treatment are unknown.

HYPERTENSION, DIABETES, AND VASCULAR DISEASE

Multiple chronic diseases have been associated with memory impairment. Hypertension (high blood pressure) and heart disease affect almost one third of today's older population.¹⁹ Hypertension and other forms of vascular disease may contribute heavily to vascular (multi-infarct) dementia, the second most common form of age-related dementia, which accounts for approximately 15% of all late-life dementias.²³ Blood pressure control is important to a person's overall health, and effective treatment of hypertension is likely to prevent cognitive decline by reducing the risk of stroke.⁸² More research is needed to definitively determine whether treatment of hypertension prevents cognitive decline. Conditions associated with heart disease, such as atrial fibrillation, myocardial infarction, and congestive heart failure, have been linked to cognitive decline.^{83,84}

Vascular dementia --- A condition caused by multiple mini-strokes that result in brain damage and loss of cognitive function. It is the second most common type of dementia. Risk factors for this condition include myocardial infarction (heart attack), hypertension (high blood pressure), atherosclerosis, diabetes mellitus, obesity, a sedentary lifestyle, and smoking.

Daily low-dose aspirin therapy is often recommended for people at risk for heart attack and stroke. Some research has shown that aspirin is moderately beneficial in preventing cognitive decline.⁸⁵ Other studies do not show a difference between aspirin users and nonusers.⁸⁶ Atherosclerosis is also a risk factor for dementia and has been shown to be associated with poor cognitive function.⁸⁷ Therefore, eating a low-fat diet and, if necessary, taking cholesterol-lowering medication to control this condition may protect against cognitive decline. More research is needed to assess whether treatment of atherosclerosis will improve cognitive functioning.

Diabetes, a common condition in older people, is a significant cause of sickness and death. Older people with diabetes may have impaired cognitive function.²⁹ However, the issue of the relationship between cognition and elevated glucose (blood sugar) levels in diabetes is difficult to interpret, since the brain needs glucose for cognition.⁸⁸ Glucose, which is the body's main source of energy and is produced from digested food, such as starch, cane sugar, maltose, and lactose, has been shown to be effective in enhancing cognitive performance in healthy young and older adults as well as in individuals with Alzheimer's disease.⁸⁹ Research suggests that cognition may be impaired in hypoglycemia

(low blood sugar) and in hyperglycemia (high blood sugar), both complications of diabetes.⁹⁰ Indeed, poor metabolic control (sustained hyperglycemia) in people with diabetes has been linked to reduced cognitive functioning.⁹¹ Given this relationship, studies of new drugs for treating diabetes should include cognitive function as an endpoint, especially if these drugs are likely to cause hypoglycemia. Furthermore, diabetes and poor control of blood glucose levels have been shown to contribute to cardiovascular disease and stroke, which are also risk factors for impaired cognitive functioning.⁹² People with diabetes should avoid both hyperglycemia and hypoglycemia in order to preserve cognitive function.

SUMMARY OF RECOMMENDED APPROACHES TO MAINTAINING COGNITIVE VITALITY

The varied approaches to achieving and maintaining cognitive vitality that have been discussed are summarized in practical terms in the following table.

BEHAVIORS THAT MAY PROTECT AGAINST COGNITIVE DECLINE

- Keep challenging yourself to learn new things (“Use it or lose it”)
- Stay physically active (“Move it or lose it” may be truer than we realize!)
- Remain socially active
- Participate in leisure activities. Practice daily stress-reduction techniques, such as meditation and/or yoga. Get a restful night’s sleep when possible
- Seek out the help you need if you suffer from depression, grief, or loneliness
- Eat well, but not too much; keep calorie intake moderate. Eat antioxidant-rich fruits and vegetables
- Take a daily multivitamin/mineral supplement but avoid taking excessive amounts
- Be safe and avoid head trauma—fasten seat belts, use a bike helmet and other safety gear, and avoid “heading”. Boxing is strongly associated with a risk of brain injury and dementia
- If you smoke, stop!
- If you drink, use alcohol in moderation—less is probably better. Do not take dehydroepiandrosterone (DHEA), human growth hormone, melatonin, or other over-the-counter anti-aging supplements without consulting your physician
- Make sure you receive proper treatment if you have high blood pressure, high cholesterol, or other cardiovascular conditions
- Make sure to keep diabetes, heart disease, and other medical conditions under control
- Use sensory aids (hearing aids, reading glasses, etc.) to maximize interaction with the environment
- If you are a woman, consider estrogen replacement therapy carefully and discuss it with your doctor

PATHOLOGIC CHANGES LEADING TO COGNITIVE DYSFUNCTION AND POSSIBLE THERAPEUTIC INTERVENTIONS

Pathologic Change

Reduced neurotransmitter production/function
(fewer or weaker signals between nerves)

Formation of senile plaques

Neural dysfunction/cell death

Decreased hormonal function

Inflammation
Oxidative stress/free radical production
Elevated homocysteine levels

Therapeutic Intervention Cognitive Enhancers

Acetylcholinesterase inhibitors^{*93-98}

Nicotinic agonists⁹⁹
Glutamate modulators^{93,100-102}
Muscarinic (M1) agonists¹⁰³
Muscarinic (M2) antagonists¹⁰³
Huperzine A¹⁰⁴
Gingko biloba¹⁰⁵
CREB[†] enhancers¹⁰⁶⁻¹⁰⁸

Disease Modifying Agents

Amyloid vaccine¹⁰⁹
Inhibitors of synthesis and production of
beta-amyloid precursor¹¹⁰
Beta and gamma secretase inhibitors¹¹⁰
Alpha secretase enhancers
Inhibitors of amyloid fibrillogenesis and aggregation

Glutamate antagonists
Neurotrophins (NGF, BDNF, AIT-082)¹¹¹⁻¹¹⁴
Caspase inhibitors
Glucocorticoid antagonists

Estrogen replacement^{17,115-122}
Testosterone replacement^{123,124}
Other hormones:DHEA[†], melatonin^{19,81,125,126}

Anti-inflammatory agents (e.g., NSAIDs[§])^{127,128}
Antioxidants (e.g., vitamin E,vitamin C)^{129,130}
Nutritional supplements
(vitamin B6, vitamin B12, and folate)

*These are the only types of drugs approved by the Food and Drug Administration for treatment of Alzheimer’s disease.
†Cyclic response-element binding protein. ‡Dehydroepiandrosterone. §Nonsteroidal anti-inflammatory drugs.

THE FUTURE OF DRUG THERAPY TO MAINTAIN COGNITIVE VITALITY

Three medications (all acetylcholinesterase inhibitors) are available and several are currently under development for the treatment of cognitive disorders and Alzheimer's disease. These medications fall into several categories based on which part of the Alzheimer's disease process they target.

Most of these types of medications are being examined for treatment of dementia, but some are under study for earlier stages of cognitive decline, particularly the MCI stage.¹²⁰ But what about drugs to improve cognition in people who do not have MCI or Alzheimer's disease but are primarily suffering from "normal cognitive aging"? Disease-modifying agents may be useful to prevent Alzheimer's disease and cognitive decline with aging, but much research needs to be done.

Some interest is growing in this area of cognitive enhancement.⁵ An example of a cognitive enhancer is cyclic AMP response-element binding protein (CREB). With cognitive training this protein is produced in the brain. Its expression has been linked to long-term memory formation in animals.¹⁰⁶ Eventually, scientists may be able to develop methods of enhancing brain levels of proteins, such as CREB, that might reduce the amount of time and effort needed to commit things to long-term memory. However, the ethics of using cognitive enhancers, such as Ritalin®, in the general population is an issue of debate because their long-term effects are unknown. Double-blind, placebo-controlled trials to test the effects of drugs on cognitive decline and dementia are necessary before drugs can be prescribed to treat these conditions.

FUTURE DIRECTIONS FOR COGNITIVE HEALTH

Our rapidly aging population requires us, as a society, to make fundamental changes in policy and research to ensure that older adults maintain the level of cognitive vitality needed to lead productive, satisfying lives.

Health care practitioners can contribute to the promotion of cognitive vitality in the following ways:

- Make cognitive vitality an important goal. Practitioners should talk with patients about how different conditions or treatments affect their minds. Some patients may become motivated to change their behavior (such as smoking) or to take medications to improve other conditions (such as diabetes or hypertension), if they think those interventions will keep their cognitive faculties intact.
- Do not assume that the cognitively impaired patient cannot be treated. All individuals reporting cognitive changes with aging should be evaluated. Practitioners should look first for causes of potentially reversible impairment and treat them. If there are none, patients should be referred for a diagnostic exam. Relatives of dementia patients should be directed to the Alzheimer's Disease Education and Referral Center (ADEAR) and the Alzheimer's Association for information and support services.
- Make sure patients do not have unrecognized or untreated sensory impairments that contribute to their problems. Practitioners should also use technologies that help those with sensory impairment to interact with their environment (e.g., hearing aids).¹³¹

Society at large can promote educational endeavors and implement policy changes to help its members achieve and maintain cognitive vitality. Some of these changes can be instituted by community organizations; others require the government to change its policies and promote

new types of funding. Specific interventions include the following:

- Local communities should institute “get-up-off-your-apathy” agendas to encourage people to get moving intellectually, physically, and socially as a means of promoting cognitive vitality.
- The government should support the development of a national population database that studies people longitudinally (over time) to assess cognitive function.¹ Diagnosis of patients for inclusion in such a study should be covered under diagnostic-related group (DRG) codes. A concerted effort should be made to include cognitive outcome measures in health-related longitudinal studies (e.g., longitudinal cardiovascular studies).
- The NIA should continue to develop interdisciplinary consortia to encourage researchers with different areas of expertise to come together to address the research issues related to achieving and maintaining cognitive vitality,^{1,132} in addition to, but separate from, the considerable amount of funding currently directed to Alzheimer’s disease. Such concerted research efforts should continue to be used for studies such as the NIA Baltimore Longitudinal Study of Aging.

Researchers also need to target specific objectives to advance knowledge about cognitive vitality. The following will facilitate the study of certain issues:

- Better description of the specific physical changes that occur in the brain with normal aging and those that occur in older people with MCI. These changes should be examined on the molecular, cellular, organ system, and individual level.
- Genetic studies. The role of genetic factors requires further study.
- Sensitive biologic markers of normal cognitive decline.¹ Measures of patient behavior are often

not sensitive enough to track changes over time, particularly with cognitive therapies. Biologic markers that can be used in this way need to be developed.

- Additional postmortem studies. Psychological tests conducted over the course of normal aging should be paired with autopsy results so that the functional changes can be linked to anatomic changes.¹³²
- Animal studies. Better animal models of normal cognitive aging need to be developed. A rapid test for cognitive impairment in the rat should be developed. Aging models and testing should be standardized across laboratories doing cognition research. Improved imaging systems are needed so that small animal brains can be examined.
- Examination of the effects that social and cultural conditions (i.e., education, early life experiences, sense of control or worth, etc.) have on cognitive vitality later in life.
- Double-blind, placebo-controlled clinical trials to assess the effects of putative agents on cognitive decline and dementia.

CONCLUSIONS

Cognitive vitality is critical to optimal aging. Although many questions about the aging brain remain, we now have suggestions for preventive strategies and interventions that promote cognitive vitality. With these in mind, people can take concrete steps to maintain their intellectual vigor. Physicians and other health care providers can play a major role in assisting individuals to achieve and maintain cognitive vitality. As our knowledge base increases, the options for promoting cognitive health are also likely to expand to meet the demands of a growing number of people who will want to remain cognitively vital in their later years.

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