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Genes, Lifestyles, and Crossword Puzzles: Can Alzheimer's Disease be Prevented?



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Introduction

These days, it seems that newspapers, magazines, and TV are full of stories about ways to stay healthy, eat right, and keep fit. Lots of people are concerned about staying healthy as they get older. They wonder whether they can do anything to prevent diseases that happen more often with age, such as Alzheimer's disease (AD).

AD has no known cure, and the secrets to preventing it are not yet known. But research supported by the National Institute on Aging (NIA) and other public and private agencies offers tantalizing clues about the origins and development of AD. These findings are raising hopes that someday it might be possible to delay the onset of AD, slow its progress, or even prevent it altogether. Delaying by even 5 years the time when AD symptoms begin could greatly reduce the number of people who have the disease.

The National Institute on Aging, part of the Federal Government's National Institutes of Health, has primary responsibility for research on AD and age-related decline in cognitive abilities (such as thinking, decision-making, and language skills). This responsibility is part of a larger mission to understand the nature of aging and find ways to help people stay physically, emotionally, and cognitively healthy for as long as possible.

Several years ago, NIA, the National Institute of Mental Health, and the National Institute of Neurological Disorders and Stroke launched The Cognitive and Emotional Health Project, which has begun to identify and describe the diverse lifestyle factors that possibly affect the emotional health and cognitive abilities of older adults. Further research on the most promising factors will be necessary to determine whether any will result in strategies that can help people remain mentally and emotionally vibrant as they age. The hope is that successful strategies will also contribute to our knowledge of what goes wrong in the brain during the development of neurodegenerative diseases like AD.



Preventing a Complex Disease Like AD is a Challenge

Many diseases, such as diabetes, heart disease, and arthritis, are complex. They develop when genetic, environmental, and lifestyle factors work together to cause a disease process to start and then progress. The importance of these factors may differ for each person. AD is one of these complex diseases. It develops over many years, and it appears to be affected by a number of factors that may increase or decrease a person's risk of developing the disease. We don't have control over some of the risk factors for AD. We can do something about other possible AD risk factors, though. The effect on any particular person of risk factor changes will likely depend on his or her genetic makeup, environment, and lifestyle.

AD Risk Factors We Can't Control

Age is the most important known risk factor for AD. The risk of developing the disease doubles every 5 years over age 65. Several studies estimate that up to half the people older than 85 have AD. These facts are significant because of the growing number of people 65 and older. More than 34 million Americans are now 65 or older. Even more significant, the group with the highest risk of AD—those older than 85—is the fastest growing population group in the country.

Genetics is the other known AD risk factor that a person can't control. Scientists have found genetic links to the two forms of AD. Early-onset AD is a very rare form of the disease that can occur in people between the ages of 30 and 65. In the 1980s and early

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1990s, researchers found that mutations (or changes) in certain genes on three chromosomes cause early-onset AD. If a parent has any of these genetic mutations, his or her child has a 50-50 chance of inheriting the mutant gene and developing early-onset AD.

Late-onset AD, the more common form, develops after age 65. In 1992, researchers found that certain forms of the apolipoprotein E (APOE) gene can influence AD risk:

- ◆ APOE ε2, a rarely occurring form, may provide some protection;
- ◆ APOE ε3, the most common form, plays a neutral role; and
- ◆ APOE ε4, which is found in about 40 percent of people with AD; APOE ε4 lowers the age of onset and thus increases risk. (Having this gene form does not mean that a person will definitely develop AD; it only increases risk. Many people who develop AD do not have the APOE ε4 form.)

Researchers are now intensively searching for other risk factor genes that may be linked to late-onset AD. Discovering these genes is essential for understanding the very early biological steps leading to AD and for pinpointing targets for drug development and other prevention or treatment strategies. It's also critical for developing better ways to identify people at risk and determining how AD risk factor genes may interact with other genes or with lifestyle or environmental factors to affect AD risk in any one individual.

In 2003, the NIA announced a major expansion of AD genetics research efforts. The AD Genetics Study is collecting genetic material from individuals in families with two or more living brothers or sisters who have late-onset AD. This valuable resource





will allow geneticists to speed up the discovery of additional AD risk factor genes.

The Search for AD Prevention Strategies

Though we can't do much about our age or genetic profile, recent research suggests that maintaining good overall health habits may help lower the chances of developing several serious diseases, including ones affecting the brain. This booklet describes a number of health, lifestyle, and environmental factors that could make a difference in AD and that are being actively studied by scientists.

Many of these potential factors have been identified in observational and animal studies. At present, they are only associated with changes in AD risk. Only further research, including clinical trials, will reveal whether, in fact, these factors can help to prevent AD. It is important to understand that the degree to which a person might be helped by any of these factors may be very slight, especially if the person has inherited a bad form of a risk factor gene. That is why it is so important to also focus on other parts of the AD prevention research mission. At the same time that scientists are examining lifestyle factors, many others are developing drugs that can enhance protective biochemical pathways or block pathways that lead to cognitive decline and AD.

Investigating heart disease risk. High levels of blood cholesterol are a known risk factor for heart disease. In recent years, basic research in laboratories as well as population and animal studies have suggested there may also be a connection between high levels of blood cholesterol and development of AD. These findings led scientists to wonder whether drugs that lower blood cholesterol

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might also lower the risk of developing AD or reduce its rate of progression. Recent population and animal studies have raised the possibility that statins, the most commonly prescribed cholesterol lowering drugs, may reduce the risk of dementia. Other studies, though, have found no association between statins and dementia risk. Thus, it is not clear at this time whether statins affect the onset or progression of AD. To help answer this question, the NIA is currently funding a clinical trial to determine whether one particular statin slows the progression of AD.

Other research has found that a high level of the amino acid homocysteine is associated with an increased risk of developing AD. High levels of homocysteine are known to increase heart disease risk, and NIA studies in mice have shown that high levels of this amino acid can make neurons stop working and die. The relationship between AD risk and homocysteine levels is particularly appealing because blood levels of homocysteine can be reduced by increasing intake of folic acid and vitamins B6 and B12. An NIA-funded clinical trial is currently studying whether reducing homocysteine levels with folic acid and vitamin B6 and B12 supplements will slow the rate of cognitive decline in older adults with AD.

Examining high blood pressure. Scientists also have found associations among AD, high blood pressure that begins in midlife, and other risk factors of stroke, such as age, diabetes, and cardiovascular disease. It is known that even in relatively healthy older adults, high blood pressure and other stroke risk factors can damage blood vessels in the brain and reduce the brain's oxygen supply. This damage may disrupt nerve cell circuits that are thought to be important to decision-making, memory, and verbal skills. Scientists are studying





the connections between AD and high blood pressure in hopes that knowledge gained will provide new insights into both conditions.

Learning about diabetes and insulin resistance. Large-scale population studies suggest that diabetes is associated with several types of dementia, including AD and vascular dementia (a type of dementia associated with strokes, sometimes referred to as multi-infarct dementia). These studies have found that AD and type 2 diabetes share several characteristics, including increasing prevalence with age, genetic predisposition, and deposits of two different kinds of damaging amyloid protein (in the brain for AD and in the pancreas for type 2 diabetes). Abnormal glucose (a type of sugar) regulation, a key element of diabetes, also has been associated with development of AD. Scientists are working to learn more about this association.

Researchers also are becoming increasingly interested in the possible role of insulin resistance (a condition in which the body produces insulin but cells do not use it properly) in AD. Too much insulin in the blood (which happens as a result of insulin resistance) may encourage inflammation and oxidative stress, both of which contribute to the damage seen in AD.

Possible relationships between cognitive decline, AD, and diabetes are being explored in the Religious Orders Study, which involves a large group of older priests, nuns, and brothers who have been working with scientists funded by the NIA since 1993. This study has provided a wealth of information about many aspects of AD, including the possible link between diabetes and cognitive decline and AD. In one analysis involving more than 800 study participants, researchers examined tests of five “cognitive systems”

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involved with word and event memory, information processing speed, and the ability to recognize spatial patterns. They found that diabetes was associated with declines in some cognitive systems but not others. The researchers also found a link between those with diabetes and an increased risk of developing AD.

The NIA is funding several clinical trials to determine whether treating different aspects of diabetes might affect AD development or progression. For example, the NIA is supporting clinical trials to evaluate the effect of a drug called rosiglitazone on changes in cognitive abilities in people with mild cognitive impairment (MCI, a condition in which a person has memory problems but not other AD problems; this condition often progresses to AD). Rosiglitazone makes cells more sensitive to insulin. The NIA is also supporting a study that is evaluating cognitive and brain structure changes using magnetic resonance imaging (MRI). This study, called ACCORD-MIND (Memory in Diabetes) has been added to the ongoing National Heart, Lung, and Blood Institute ACCORD (Action to Control Cardiovascular Risk in Diabetes) clinical trial. ACCORD is evaluating a variety of approaches for managing glucose, blood pressure, and blood lipids.

Examining social engagement and intellectually stimulating activities. Findings from studies of animals, nursing home residents, and older people living in the community have suggested a link between social engagement and cognitive abilities. Having lots of friends and acquaintances and participating in many social activities is associated with reduced cognitive decline and decreased risk of dementia in older adults. In the NIA-funded Chicago Health and Aging Project, a high level of social engagement was associated with a significant reduction in cognitive decline.





Studies also have shown that keeping the brain active is associated with reduced AD risk. In the Religious Orders Study, for example, investigators periodically asked more than 700 participants to describe the amount of time they spent in seven activities that involve significant information processing. These activities included listening to the radio, reading newspapers, playing puzzle games, and going to museums. After following the participants for 4 years, investigators found that the risk of developing AD was 47 percent lower, on average, for those who did the activities most frequently than for those who did them least frequently. Other studies have shown similar results. In addition, a growing body of research, including other findings from the Religious Orders Study, suggests that, even in the presence of AD plaques, the more formal education a person has, the better his or her memory and learning ability.

Another NIA-funded study also supports the value of lifelong learning and mentally stimulating activity. In this study of healthy older people and people with possible or probable AD, scientists found that during their early and middle adulthood, the healthy older people had engaged in more mentally stimulating activities and spent more hours doing them than did those who ultimately developed AD.

The reasons for these findings aren't entirely clear, but scientists have come up with four possibilities:

- ◆ These activities may protect the brain in some way, perhaps by establishing a “cognitive reserve.”
- ◆ Perhaps these activities help the brain become more adaptable and flexible in some areas of mental function so that it can compensate for declines in other areas.

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- ◆ Less engagement with other people or in intellectually stimulating activities could be the result of very early effects of the disease rather than its cause.
- ◆ Perhaps people who engage in these activities have other lifestyle features that may protect them against developing AD.

The only way to really evaluate some of these possibilities is by testing them in a controlled way in a clinical trial.

Several clinical trials have directly examined whether memory training and similar types of mental skills training can actually improve the cognitive abilities of healthy older adults and people with mild AD. In the Advanced Cognitive Training for Independent and Vital Elderly (ACTIVE) trial, certified trainers provided 10 sessions of memory training, reasoning training, or speed of processing training to healthy adults 65 years old and older. The sessions improved participants' mental skills in the area in which they were trained. Even better, these improvements persisted for at least 2 years after the training was completed. In another study, 25 participants with mild AD worked with researchers to learn how to improve their ability to carry out various tasks, such as how to put names and faces together, recall the names of objects, and pay bills correctly. Compared to another group with mild AD who received more generic mental stimulation activities, people in the "cognitive rehabilitation" group improved their abilities more, and their abilities were still improved 3 months later.

Investigating physical activity. Accumulating evidence suggests that being physically active may benefit more than just our hearts and waistlines. Research in older animals has shown that both physical and mental function improve with aerobic fitness. Two





studies in aging adults have shown similar results. The first study used MRI to measure changes in brain activity in healthy adults aged 58-78 before and after a 6-month program of brisk walking. The researchers found that improvements in the participants' cardiovascular fitness were associated with increased functioning in certain regions of the brain. Compared to a physically inactive group, the walkers were able to pay attention better and focus more clearly on goals while disregarding unimportant information.

In a second study, investigators studied the relationship of physical activity and mental function in nearly 6,000 healthy women 65 years old and older over a period of up to 8 years. The investigators found that the women who were more physically active were less likely to experience a decline in their mental function than were inactive women. The NIA is currently funding several clinical trials that are studying the effects of physical activity programs on the cognitive abilities and brain function of healthy older adults and older adults with MCI.

Scientists have speculated about why physical activity may help our brains as much as our bodies. It may be that physical activity improves blood flow to the brain so that it responds better to a task. Or, it may activate cellular mechanisms that improve brain function. However, we still don't know whether physical activity can actually prevent cognitive decline or postpone the development of AD, especially in people with a high genetic risk.

Examining nonsteroidal anti-inflammatory drugs (NSAIDs).

Inflammation of tissues in the brain is a common feature of AD, but it is not clear whether it is a cause or effect of the disease. Some population studies suggest an association between a reduced

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risk of AD and commonly used NSAIDs, such as ibuprofen, naproxen, and indomethacin.

Clinical trials thus far have not demonstrated a benefit for AD from these drugs or from the newer cyclooxygenase-2 (COX-2) inhibitors, such as rofecoxib and celecoxib. A trial testing whether naproxen or celecoxib could prevent AD in healthy older people at risk of the disease has been halted, but investigators are continuing to conduct follow-up examinations with participants and to examine data about cognitive changes and possible cardiovascular risk. Scientists continue to look for ways to test how anti-inflammatory drugs targeting particular pathways might affect the development or progression of AD.

Learning about antioxidants and other interventions. Another promising area of research focuses on highly active molecules called free radicals. Damage from these free radicals during aging can build up in nerve cells and result in a loss of cell function, which could contribute to AD. Some population and laboratory studies suggest that antioxidants from dietary supplements or food may provide some protection against this damage (called oxidative damage), but other studies show no effect.

Clinical trials may provide some answers. Several trials are investigating whether two antioxidants—vitamins E and C—can slow cognitive decline and development of AD in healthy older individuals. The NIA is conducting a clinical trial that will examine whether taking vitamin E and/or selenium supplements over a period of 7 to 12 years can help prevent memory loss and dementia. This trial has been added on to a prostate cancer prevention clinical trial funded by the National Cancer Institute. The NIA





is also conducting a clinical trial to determine whether antioxidant supplements can prevent cognitive decline in healthy older women or older women at increased risk of dementia.

Another just-completed study focused on the use of vitamin E supplements in people with MCI. This NIA study, the Memory Impairment Study, compared donepezil (Aricept), vitamin E supplements, or placebo (an inactive substance) in participants with MCI to see whether the drugs might delay or prevent progression to AD. The study found that taking the vitamin E had no effect on progression to AD at any time in the study when compared with placebo. It may be that this antioxidant may not help after memory declines have already started. Donepezil, however, did seem to delay progression to AD over the first year of treatment. Interestingly, there seemed to be an interaction between the genetic makeup of participants and their response to treatment: People carrying the risk factor APOE ϵ 4 allele delayed the risk of developing AD for the 3 years of the trial. Scientists caution, however, that people with MCI should not be tested to see whether they carry the APOE- ϵ 4 allele because more research is still needed to understand how the drug works in the body and to answer other questions.

Expanding knowledge about estrogen. This hormone is produced by a woman's ovaries during her childbearing years. After this time, estrogen production declines dramatically. Over the past 25 years, some laboratory and animal research, as well as observational studies in women, have suggested that estrogen used by women to treat the symptoms of menopause also protects the brain. Experts have wondered whether using estrogen could reduce the risk of AD or slow disease progression.

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A number of clinical trials have shown that estrogen does not slow the progression of already-diagnosed AD. Clinical trials testing whether estrogen might prevent AD in women who have already gone through menopause have also found that using estrogen to treat or prevent AD may not be effective, if treatment is begun in later life. A large trial found that women older than 65 who took estrogen (Premarin) alone or estrogen with a synthetic progestin were actually at increased risk of developing dementia, including AD. Some questions remain unanswered, however, such as whether some forms of estrogen might help if started somewhat earlier than the older ages tested in this trial. These questions are now being investigated.

Researchers also are trying other ways to work with estrogen's potentially positive effects for the brain. For example, scientists have developed estrogen-like molecules called SERMs (selective estrogen-receptor modulators) that protect against bone loss and other consequences of estrogen levels falling after menopause. These molecules may retain estrogen's neuron-protecting ability but may not have some of its other harmful effects on the body. A large clinical trial tested a SERM called raloxifene, which is used in the prevention and treatment of osteoporosis. The study showed that this SERM lowered the risk of MCI among a group of post-menopausal women with osteoporosis. A newly-funded clinical trial is ongoing to test whether raloxifene can slow the rate of AD progression.

Investigating *ginkgo biloba*. This readily available natural product has been proposed as a potential treatment or preventive agent for AD. A 1997 study in the U.S. suggested that a ginkgo extract may be of some help in treating the symptoms of AD and multi-infarct





dementia, but no evidence exists that *ginkgo biloba* will prevent AD. At the NIH, the National Center for Complementary and Alternative Medicine and the NIA are currently supporting a large clinical trial to explore whether ginkgo has any effect on preventing AD or delaying cognitive decline in older adults.

Exploring immunization. Will a vaccine someday prevent AD? Early vaccine studies in mice were so successful in reducing deposits of beta-amyloid (the major component of the plaques that develop in the brains of people with AD) and improving brain performance on memory tests that investigators conducted preliminary clinical trials in humans with AD. These studies had to be stopped because of life-threatening inflammation that occurred in some participants. However, the pharmaceutical industry and NIH-funded scientists are continuing to refine this strategy in animal models of AD, hoping to find ways of maintaining the therapeutic effects while reducing the unwanted side effects. Several pharmaceutical companies have recently obtained permission from the FDA to test several of these new strategies for safety in early stage clinical trials.

The Search for Other Clues That May Contribute to Prevention Strategies

Investigators are pursuing still other strategies that may eventually help to prevent or delay AD. For example, they are trying to discover whether changes in certain biological compounds in blood, urine, or cerebrospinal fluid could indicate early AD changes in the brain. Understanding more about these biological markers, how they work, and what causes their levels to change is important in

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helping scientists answer questions about what makes AD begin and develop. Learning more about these markers also may help scientists track whether certain medications are having their intended effects and may some day lead to new prevention strategies.

One major effort involves the use of imaging techniques, such as MRI and positron emission tomography (PET), to measure brain structure and function. An NIA public-private partnership—the AD Neuroimaging Initiative—is a large study that will determine whether MRI and PET scans or other imaging or biological markers can be used to identify early AD changes and disease progression. One day, these measurements may be able to identify those people who are at risk of AD before they develop symptoms. The measurements may also help physicians assess the response to treatment much more rapidly and less expensively than is possible today. To learn more about the Neuroimaging Initiative, visit the NIA's Alzheimer's Disease Education and Referral Center (ADEAR) at www.alzheimers.nia.nih.gov, or call the ADEAR Center toll-free at 1-800-438-4380.

What Can You Do?

Our knowledge is growing rapidly as scientists expand their understanding of the many factors involved in the development of AD. Even though no treatments, drugs, or pills have yet been proven to prevent AD or even delay its development, people can take some actions that might reduce the effect of possible AD risk factors. These actions include:

- ◆ lowering cholesterol and homocysteine levels

- ◆ lowering high blood pressure levels
- ◆ controlling diabetes
- ◆ exercising regularly
- ◆ engaging in social and intellectually stimulating activities

All of these strategies are good to do anyway because they lower risk of other diseases and help maintain and improve overall health and well-being. However, it is important to remember that pursuing any of these strategies will not necessarily prevent or delay AD in any one individual. Even if the strategies were eventually proven to be effective, they might not offset a person's individual genetic and other risk factors enough to prevent AD from developing.

Another important action a person can take is to volunteer for the Genetics Study, the Neuroimaging Initiative, or an AD clinical trial. People who participate in these studies say that the biggest benefit is having regular contact with experts on AD who have lots of practical experience and a broad perspective on the disease. They also feel they are making a valuable contribution to future knowledge that will help scientists, people with AD, and their families. Families interested in participating in the Genetics Study can call the National Cell Repository for Alzheimer's Disease (NCRAD) toll-free at 1-800-526-2839. Information may also be requested through its website at <http://ncrad.iu.edu>. People who are interested in joining the Neuroimaging Initiative or an AD clinical trial should contact the ADEAR Center at www.alzheimers.nia.nih.gov, or call the ADEAR Center toll-free at 1-800-438-4380 for a referral to the nearest participating study site.

A Final Word of Caution

Because AD is such a devastating disease, caregivers and patients may be tempted by untried, unproven, and unscientific cures, supplements, or prevention strategies. Before trying pills or anything else that promises to prevent AD, people should check with their doctor first. These purchases might be unsafe or a waste of money. They might even interfere with other medical treatments that have been prescribed.

For More Information

Becoming well informed is another important thing that people can do to protect their health. Thousands of Internet websites provide health-related information, including information on AD.

Some of the information on these websites is reliable, but some is not. Health websites sponsored by the Federal Government are good sources of information, as are websites of large professional organizations and well-known medical schools. Some excellent Internet sources of AD and other health-related information for consumers are:

Alzheimer's Disease Education and Referral (ADEAR) Center

P.O. Box 8250
Silver Spring, MD 20907-8250
1-800-438-4380
www.alzheimers.nia.nih.gov

This service of the NIA offers information and publications on diagnosis, treatment, patient care, caregiver needs, long-term care, education and training, and research related to AD. The ADEAR Center provides several easy-to-understand publications that explain memory loss and AD, highlight ongoing research, and describe efforts to support AD caregivers. Other publications, including the *Progress Report on Alzheimer's Disease*, provide a more comprehensive update on NIH's AD research effort. These and other ADEAR publications can be previewed and ordered on the website. Staff at the ADEAR Center also respond to information requests and make referrals to local and national resources. The Center also maintains a database of AD clinical trials and studies and can answer questions about where particular ones are being conducted.

Alzheimer's Association

225 N. Michigan Avenue, Suite 1700
Chicago, IL 60601-7633
1-800-272-3900
www.alz.org

This nonprofit association supports families and caregivers of patients with AD and funds AD research. Chapters nationwide provide referrals to local resources and services, and sponsor support groups and educational programs.

National Institute on Aging Information Center

P.O. Box 8057
Gaithersburg, MD 20898-8057
1-800-222-2225
1-800-222-4225 (TTY)
www.nia.nih.gov

Visit: www.nia.nih.gov/HealthInformation to order publications (in English or Spanish) or sign up for regular email alerts.

Visit NIHSeniorHealth.gov (www.nihseniorhealth.gov), a senior-friendly website from the National Institute on Aging and the National Library of Medicine. This simple-to-use website features popular health topics for older adults. It has large type and a “talking” function that reads the text out loud.

For additional copies of this publication or further information
on Alzheimer's disease, please contact:

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