

ALZHEIMER'S DISEASE AND RISK FACTORS

What is Alzheimer's disease?

Alzheimer's disease is the most common of a large group of disorders known as "dementias." It is an irreversible disease of the brain in which the progressive degeneration of brain cells causes thinking ability and memory to deteriorate. Alzheimer's disease also affects behaviour, mood and emotions, and the ability to perform daily living activities.

There is currently no cure for Alzheimer's disease, but there are treatment options and lifestyle choices that can slow its progression. Also, the pursuit of new research strategies should one day help restore some lost function and memory.

Alzheimer's disease progresses through early, middle and late stages before reaching the final end of life stage. However, identifying the transition from one stage to another is often difficult. Not only does the disease usually progress slowly, but the symptoms related to each stage tend to overlap and the order in which they appear and how long they last varies from person to person.

The duration following diagnosis is usually seven to ten years. However, when the diagnosis is delayed, as it may be if the affected person fails to see a doctor early on, the disease duration is shorter than this. Conversely, as the ability to diagnose Alzheimer's disease improves and people become more willing to be assessed, survival times following diagnosis are lengthening.

Other dementias

"Other dementias" resemble Alzheimer's disease in that they also involve a progressive degeneration of brain cells that is currently irreversible. They include the dementia associated with Vascular dementia (the second

most common dementia after Alzheimer's disease), Frontotemporal dementia, Creutzfeldt-Jakob disease, Lewy body dementia, Parkinson's disease, and Huntington disease.

Other dementias (reversible dementias)

A small percentage of dementias are reversible, occurring as a secondary development in treatable conditions. Toxic reactions to prescription or over the counter medications are the most common cause of reversible dementia. Others include dietary or vitamin B12 deficiencies, infections, tumours, alcoholism, inflammatory states, hormonal dysfunction, environmental toxins, drug abuse, and depression.

How is Alzheimer's disease diagnosed?

In considering the diagnosis of Alzheimer's disease clinicians first make a thorough examination of the person's general physical status to exclude the reversible conditions mentioned above. If there are no indications that any of these conditions are involved, a full family history is undertaken and the behaviours that are most affected are noted (e.g. an impaired ability to learn and remember new things, to speak normally, to comprehend or respond appropriately, or to find the way in familiar surroundings). The rates at which impairments develop are important in distinguishing which dementia is present.

The examination will include a number of mental status, memory and cognitive tests (such as the widely-used Clock Drawing Test and the Mini-Mental State Examination (MMSE)). These tests lead to a diagnosis that is 90-95% accurate. Testing may also include blood, liver and (occasionally) cerebrospinal fluid (CSF) tests, but these are not usually deemed necessary. When additional

testing is required, most often it is brain imaging. Brain imaging is especially useful in distinguishing between Alzheimer's disease and other dementias. Various imaging technologies such as MRI, fMRI, PET, and SPECT may be used.

What are risk factors?

Many diseases have specific causes, for example a virus causes measles. However, the causes of many chronic diseases or conditions are unknown or uncertain. In their search for answers, scientists look for factors that appear to be linked to the development of a disease. These are "risk factors" – if they are present, there is an increased chance, but not a certainty, that the disease will develop. Risk factors are characteristics of the person, their lifestyle, environment, and genetic background, which contribute to the likelihood of getting a disease. Some risk factors can be modified (e.g. lowering blood pressure); other risk factors cannot be modified (such as a person's genetic makeup).

It is important to note that risk factors are not on their own causes of a disease. In general, scientists believe that Alzheimer's disease is caused when the combined effects of the various risk factors cross a certain threshold and overwhelm the natural self-repair mechanisms in the brain, thus reducing the brain's ability to maintain healthy nerve cells.

Identification of risk factors for Alzheimer's disease is important because they can indicate lifestyle choices that can help reduce a person's chance of developing the disease. Some factors are beyond individual control, while other important risk factors can be reduced through appropriate lifestyle. See section on Reducing the risk.

How are risk factors determined?

Two types of studies are used to determine risk factors. One approach is to study people who already have the disease (in this case Alzheimer's disease) and compare them with people who are similar in age, gender and other characteristics, but who do not have the disease. This is known as a case-control study. Information is gathered on their personal and family characteristics, as well as on past exposures that may have occurred through lifestyle and work. Risk factors are identified as occurring more

frequently in those with the disease than in those without. It is important to note that risk factors are still seen in the group who do not have Alzheimer's disease, but not as often. This method was used in the first analysis of risk factors for Alzheimer's disease from the Canadian Study of Health and Aging (CSHA).¹

The second approach is to monitor a group of healthy people over a long period of time. This is known as a cohort study. From this group, people with particular characteristics (such as a tendency towards high blood pressure) or similar lifestyles (such as vegetarianism) are compared to people without those characteristics or lifestyles to detect any difference in the rate at which the two groups develop a disease. Factors that are known to be associated with a specific disease, such as obesity in the case of Alzheimer's disease, are of particular interest in cohort studies. Using these approaches, characteristics and exposures that are associated with the occurrence of the disease can be identified. This approach was used in the second analysis of risk factors for Alzheimer's disease from the Canadian Study of Health and Aging.²

What are the risk factors associated with Alzheimer's disease?

Age

Age is the most important risk factor. As we age, our body's ability to repair itself becomes less efficient. The extent by which the self-repair of our brains diminishes varies from person to person and these differences contribute to an individual's susceptibility to Alzheimer's disease as they age. As well, many of the other known risk factors for the disease tend to increase with age (such as elevated cholesterol and being overweight). However, risk factors do not cause Alzheimer's disease on their own. The brain has to reach a certain critical age for the disease to occur. The older you become the higher the risk – 1 in 20 Canadians over age 65 and 1 in 4 of those over age 85 are affected by Alzheimer's disease.

Family history and genetics

A very small percentage of people with Alzheimer's disease (5-7%) has Familial Alzheimer's disease or FAD (formerly known as "early onset Alzheimer's disease"). At some point in their family history certain genes mutated and developed the abnormal characteristics that cause

FAD. These inherited genes have a powerful influence: if one parent has FAD, each child has a 50 % chance of inheriting the disease, and with two parents with FAD, all their children will go on to develop Alzheimer's disease in adulthood. These inherited genes differentiate FAD from the more common sporadic form of Alzheimer's disease, but the disease itself is identical.

The sporadic form of Alzheimer's disease (which used to be called "late onset Alzheimer's disease"), was formerly assumed to have no family linkages. However, it's now known that a person with a direct relative (parent or sibling) with Alzheimer's disease has a three times greater chance of developing the disease than someone who does not.* The risk increases further if both parents have the disease. So aside from the FAD-related genes there are Alzheimer's disease-related genetic factors shared by family members.

New research is revealing more and more genetic risk factors for the sporadic form of Alzheimer's disease. That means that these genes are found to a greater extent among those with the disease, though they are also found in people without Alzheimer's disease. People with these genetic risk factors are not in the same high-risk category as people who have the mutated genes responsible for FAD. In fact, the risk associated with any one of these newly discovered genetic risk factors is lower than the risk associated with having a parent with the sporadic form of the disease (with the exception of the apoE4 gene discussed below).

Please refer to the Alzheimer Society's Information Sheet on **Alzheimer's disease and Genetics** for more information.

ApoE4 gene

This gene is the most important genetic risk factor for the sporadic form of Alzheimer's disease. ApoE genes regulate the production of a protein that helps carry cholesterol and other fats in the blood to the cells of the body. Of the three variants of the apoE gene (apoE2, apoE3 and apoE4), the apoE4 variant is associated with an increased risk of Alzheimer's disease.

In our cells (except ova and sperm) all genes are paired, one being contributed by the father and one by the mother. If a person's pair of apoE genes includes one apoE4 gene, their risk of developing Alzheimer's disease is increased. However, approximately half of all people with two apoE4 genes will develop Alzheimer's disease at age 65. People with no apoE4 genes can still get Alzheimer's disease and people with two apoE4 genes will not necessarily get the disease.

Female gender

Twice as many women get Alzheimer's disease than men. Many believe that it is in a large part a result of the changes to women's hormones at menopause, in particular the decline of the important hormone estrogen. In the past estrogen was often prescribed to relieve symptoms of menopause and to reduce the risk of developing Alzheimer's disease. However, a fairly recent large-scale clinical study recommended discontinuation of Hormone Replacement Therapy (HRT) because of potentially dangerous side effects. A number of clinical researchers regard HRT as worthy of further study especially in the context of Alzheimer's disease. Any decision regarding the use of HRT should be made in consultation with a physician.

However, hormonal changes are not the only factor contributing to the increased incidence of Alzheimer's disease in women. On average, women live longer than men and age is a risk factor. Women are also more prone to diabetes, which is also a risk factor (see below), and recently, a gene was identified that occurs only in women, and appears to somewhat increase the risk for Alzheimer's disease.

Cardiovascular disease

All the risk factors for cardiovascular disease (such as high blood pressure and high cholesterol levels) are also risk factors for both Alzheimer's disease and Vascular dementia. Strokes and mini-strokes (the latter detected largely through later testing), are also well-accepted risk factors for Alzheimer's disease and for Vascular dementia.

* Here is a useful way of looking at the relative risk: of 100 people with no defined genetic risk factor, 5 will get Alzheimer's disease at age 65 (and 95 will not). Of 100 people, each with a parent with Alzheimer's disease, 15 will get Alzheimer's disease at age 65 (and 85 will not).

Diabetes

It has been known for some time that type 2 (“Adult”) diabetes is a risk factor for Alzheimer’s disease. It has been generally assumed that the two are linked by cardiovascular disorders, which are associated with diabetes and are risk factors for Alzheimer’s disease. It has also been known that the utilization of glucose in the brains of people with Alzheimer’s disease is impaired, somewhat resembling the situation in the bodies of people with type 2 diabetes.

An even more recent finding suggests that the Alzheimer’s brain has a diabetes-like condition that some are calling type 3 diabetes. Researchers have found that in people with Alzheimer’s disease the production of insulin in the brain is reduced and the nerve cells are less sensitive to it. (Production of insulin in the brain is independent of insulin production in the pancreas, the major insulin-producing organ). Anti-diabetic drugs that target the brain are now being tested in people with Alzheimer’s disease.

Recently evidence was also presented that children with type 1 (“Juvenile”) diabetes are at risk for developing Alzheimer’s disease in later life.

Down syndrome

Almost all individuals with Down syndrome who live into their forties and beyond will develop the abnormal changes in the brain (the plaques and tangles) that characterize Alzheimer’s disease. It is important to note, however that not all people with Down syndrome who develop these brain changes will go on to develop dementia. It seems likely that these people may not yet have developed other age-induced changes that occur in most people with Alzheimer’s disease. Please refer to the Alzheimer Society’s Information Sheet on **Alzheimer’s disease and Down syndrome** for more information.

Mild Cognitive Impairment (MCI)

In MCI, there is a level of cognitive and/or memory impairment beyond that expected for normal aging but not sufficiently advanced to be called “dementia” or “Alzheimer’s disease.” It is estimated that up to 85% of people with MCI, who are often in their early forties or fifties, will develop Alzheimer’s disease within ten years, making MCI an important risk factor for the disease. Researchers now know that the abnormal changes in the

brain characteristic of Alzheimer’s disease can begin to appear in people diagnosed with MCI twenty or more years before there are signs of dementia. Brain imaging may make it possible to detect the most at-risk individuals with MCI, and research to this end is ongoing.

Head injury

Brain injuries at any age, especially repeated concussions, are accepted by most clinicians as risk factors for the later development of Alzheimer’s disease.

Low levels of formal education

Several studies have shown that people who have less than six years of formal education appear to have a higher risk of developing Alzheimer’s disease. It has been assumed that the brain stimulation associated with learning provides a protective effect for the brain; therefore more education provides greater protection. However, new studies challenge this conclusion, and it may be that factors often associated with low educational background, such as unhealthy lifestyle, account for the risk rather than low educational level itself.

Other risk factors

In addition to the risk factors described above, all of the following have been documented as risk factors for Alzheimer’s disease: inflammatory conditions (possibly reflecting immune system malfunction), a history of episodes of clinical depression, stress, and inadequate exercising of the brain. Risk factors that are less firmly established include smoking, excessive alcohol consumption and drug abuse.

Aluminum

Most researchers no longer regard aluminum as a risk factor for Alzheimer’s disease. However, researchers are still examining whether some people are at risk because their bodies have difficulties in handling foods containing the metals copper, iron and aluminum.

Remember

Risk factors do not on their own cause Alzheimer’s disease. They suggest an increased chance but not a certainty that the disease will develop. Similarly, having little or no exposure to known risk factors does not necessarily protect a person from developing Alzheimer’s disease. Further research will help deepen our understanding of the role of risk factors in developing Alzheimer’s disease.

Reducing the risk

In studies of identical twins (who share the same genes) it was found that about **60% of the overall risk for sporadic Alzheimer's disease comes from lifestyles and not from genes**. Living a healthy lifestyle may help to reduce one's overall risk of developing Alzheimer's disease.

A healthy lifestyle includes healthy eating, maintaining a healthy weight, taking part in regular physical activity (which can be quite modest), maintaining normal blood pressure and cholesterol levels and participating in activities that involve socializing and stimulating brain activity. For more information on reducing your risk, see the Alzheimer Society's brochure, **Heads Up for Healthier Brains**.

Need further information?

Please refer to the Alzheimer Society's booklet, **A Report on Alzheimer's Disease and Current Research** by Dr. Jack Diamond, former Scientific Director, Alzheimer Society of Canada (2011). Please visit the Alzheimer Society's website at www.alzheimer.ca or contact your local Alzheimer Society.

References:

- ¹ Canadian Study of Health and Aging: Risk factors for Alzheimer's Disease in Canada. *Neurology* 1994; 44:2073-2080.
- ² Risk Factors for Alzheimer's Disease: A Prospective Analysis from the Canadian Study of Health and Aging, *American Journal of Epidemiology* 2002; Vol. 156, No. 5, 445-453.

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