Review (Narrative)

Risk Factors for Alzheimer’s Disease

Wendy L. Trepson, M.Sc.

SUMMARY

Alzheimer’s disease (AD) is the most common disease in developed countries and affects more than half of the population in low- and middle-income countries. In the past decade, studies have shown that biological and sociological factors have a significant effect on the occurrence and development of AD. Among them, genetic and environmental factors, pathophysiological characteristics, and unhealthy lifestyle factors cause the neurological symptoms. Among them, the risk factors of cognitive decline in the elderly caused by lifestyle can be intervened in the early stage. If some adults can overcome these risk factors as early as possible, they can predict that they will gradually reduce their cognitive impairment over time, and the likelihood of developing AD will decrease in the future.

KEYWORDS

Alzheimer’s disease; Cognitive Ability; Lifestyle; Risk Factors


Author Affiliations: Author affiliations are listed at the end of this article.

Correspondence to: Ms. Wendy L. Trepson, M.Sc., Intelligence Brain Institute, Carson City, NV 89701, USA. Email: wtrepson@ibi.com
ALZHEIMER’S disease (AD) is one of the common diseases in developed countries and affects more than half of the population in low- and middle-income countries. Dementia such as AD is a complex neurodegenerative disease with many related causes, involving biological and sociological risk factors. Although these factors interact with each other, the relationship between them is currently unclear. In fact, the lifestyles associated with these risks affect personal habits, which in turn affect the health of our bodies and brains. There is ample evidence that certain lifestyles herald faster cognitive decline and a higher risk of dementia, while some social and professional activities have a protective effect.

Studying the development of age-related diseases can help determine the severity and nature of nerve damage from different factors and the risk of dementia during different life processes. The main purpose of this review is to collect scientific evidence for the corresponding risks of early behavioral factors, and provide people with targeted responses to reduce the risk of AD in later life.

EFFECTS OF GENETIC AND ENVIRONMENTAL FACTORS ON ALZHEIMER’S DISEASE

Impact of Important Genes on Alzheimer’s Disease

AD is a common type of dementia, and many molecular lesions have been detected in AD: extracellular amyloid plaques formed by the accumulation of toxic beta amyloid (Aβ) and hyperphosphorylated tau protein Intra cellular neuronal fiber tangles (1).

Apolipoprotein E (Apolipoprotein E) has been one of the hot topics in the past decade. It is a polymorphic protein rich in arginine, which is mainly involved in the transformation and metabolism of lipoproteins and can regulate many biological functions. Among them, the ApoEε4 allele is the most important genetic risk factor for late-onset AD (> 65 years), accounting for 50% of genetic susceptibility. Alleles are also commonly associated with other diseases, including vascular dementia, mild cognitive impairment, elevated low-density lipoprotein, and cardiovascular disease. There are more than 550 genes thought to be related to the pathogenesis of dementia, but the relevant mechanism is not clear (2).

An in-depth study of the ApoEε4 allele provides an example of a complex gene-environment interaction. A large 21-year study found that ApoEε4 alone increased the risk of dementia due to AD by 2.83 times; taking into account lifestyle and lifestyle (including physical activity, drinking, smoking, diet, etc.) Interaction, the risk of illness was further increased to 11.42 times. Another study found that Apo Eε4(+) patients with temporal lobe dementia (FTD) have lower HDL-c, fasting blood glucose, and higher peripheral blood insulin levels, suggesting that most FTD patients with Apo Eε4(+) have insulin resistance. And Apo Eε4 gene may be related to the characteristics of abnormal eating behaviors in FTD patients. In other words, ApoEε4 carriers may be more susceptible to lifestyle influences; in turn, lifestyle interventions may significantly alter the risk of dementia.

A cross-cultural epidemiological study also supports the idea that a nutritious lifestyle may be a major driver of the risks associated with ApoEε4 carriers (3).

In addition, genetic mutation theory shows that early-onset AD, which develops before the age of 65, is related to genes on chromosome 21, especially the β-amyloid precursor gene (APP gene) and PS1 on # 1 and # 14 (Presenilin) and PS2 genes (4). At present, the mainstream theory of the pathogenesis of AD is the beta amyloid deposition theory (5).

With the gradual progress of research (6), the results show that most of the AD risk genes affect the formation and elimination of Aβ, and gene variants are involved in cholesterol metabolism and endocytosis (7).

In recent years, small molecule ribonucleic acids (miRNAs) have been found to increase expression in peripheral blood mononuclear cells from AD. A blood cell study, through next-generation sequencing, found that 12-miRNA signals can significantly distinguish between AD and control groups (8). The study of specific circulating miRNAs as diagnostic biomarkers has shown that circulating miRNAs are the next generation of promising AD biomarkers and may eventually be used to identify neurodegenerative diseases. Research in this area is expected to diagnose AD early (9).

Impact of Environmental Factors on Alzheimer’s disease

Geographical change data from the global incidence of dementia indicate (10) that environmental risk factors play an important role in the pathogenesis of dementia.
Elevated levels of nitric oxide and carbon monoxide in the environment have a dose-response relationship with the risk of dementia. Many studies have attempted to establish the relationship between toxic heavy metals in the environment and the risk of dementia (11). For example, people born in areas with higher than average lead (Pb) concentrations have an extremely high risk of AD. When the daily drinking water exceeds 0.1 μg, the intake of aluminum is positively correlated with the increased risk of dementia; however, whether calcium, cobalt, copper, iron, molybdenum, nickel, and uranium are risk factors (12) is still inconclusive. Studies have shown that zinc and selenium are important protective factors for AD (13). The neuropsychological performance of some winery workers is related to the possibility of long-term exposure to pesticides, as most wineries use biocides. However, there is no detailed research report on the risk of dementia in occupational exposure to diesel engine exhaust, lead, ink, dye, paint, gasoline, fuel, liquid plastic or rubber.

Evidence regarding the effects of exposure to low and very low frequency electric or magnetic fields is contradictory, and may be related to a certain degree to the risk of dementia (14). Studies have found that long-term living near high-voltage power lines has doubled the mortality rate caused by neurodegenerative diseases. As for the effect of increasing TV viewing time, the relevant electric and magnetic field exposures need to be considered, but no systematic research papers have been published (15).

Environmental and other non-genetic factors can activate alpha secretase in patients with dementia and increase the risk of dementia (16).

The pathogenesis of AD, in addition to biological and social factors, also has the effect of various environmental factors, which is the result of the interaction of multiple factors. With the continuous progress and development of society, new environmental exposures continue to appear, and the adverse effects that may be brought to human health are not yet recognized by humans. It is generally believed that environmental factors may affect the incidence of AD on the basis of genetic susceptibility (17).

**multiple chronic diseases are important risk factors for alzheimer’s disease**

Comprehensive research shows that there are many risk factors for AD. Among them, many chronic diseases are important risk factors for AD.

Various diseases (including diabetes, hypertension, obesity, and elevated total cholesterol) in the western world are also risk factors for cognitive decline and dementia (18). Although markers of inflammatory genetic factors related to the disease are associated with AD through complex mechanisms, insulin signaling by inflammatory interference is a common influence pathway involving various environmental factors and gene-environment interactions. In turn, interrupted insulin signals can lead to diabetes-related hyperglycemia, hyperlipidemia, and neurodegenerative processes leading to vascular disease (19).

More and more epidemiological literature confirms that chronic obesity, high cholesterol, and high systolic blood pressure are important risk factors for cognitive decline, each of which can increase the risk by about two times. In addition, the related risks may be superimposed; once all factors are combined, the overall risk of dementia will be further increased, sometimes even more than six times (20).

Studies have analyzed the correlation between diabetes and dementia, and found that the former can increase the risk of the latter (with dementia) by 50% to 100% and the risk of vascular dementia by 100% to 150%. A prospective study of older women found that not only is the risk of dementia increased (1.79 times) in patients with diabetes, but also the risk of dementia is increased in those patients who have only impaired glucose tolerance (1.64 times) (21). Similarly, a 10-year prospective study of non-diabetic women also found that higher fasting insulin levels may lead to larger values of reduced language memory. The link between hyperinsulinemia and cognitive impairment supports insulin resistance as an important factor leading to dementia (22).

Studies have reported an increased risk of dementia in patients with type 2 diabetes carrying ApoEε4 (23). In general, the mechanisms by which diabetes may increase cognitive decline and the risk of dementia include: (i) oxidative stress and an increase in amino sugar compounds, which can cause nerve damage; (ii) a decrease in glucose access, leading to acetylcholine syn-
thesis (iii) the effect of insulin on Aβ metabolism and vascular disease (24).

In addition, cerebral atrophy, cerebral infarction, hypertension, coronary heart disease and other diseases will affect the elderly’s intelligence, reduce the quality of life and life ability, and further reduce the cognitive ability of the elderly (25). Older people with a history of stroke also have a significantly increased risk of dementia (26).

**Effects of Physical Factors Such as Overweight on Alzheimer’s Disease**

Numerous epidemiological studies have linked middle-aged obesity to the high risk of dementia in later life. A 27-year prospective study from the United States evaluated the relationship between middle-aged obesity and body mass index (BMI) and the risk of dementia in later life. Middle-aged obesity increases the risk of AD. Compared with those with normal weight (BMI = 18.6–24.9), the risk of dementia in obese people (BMI ≥ 30) increased by 74%, while the risk of overweight people (BMI = 25–29.9) increased by 35%.

Increased body mass index is also associated with decreased cognitive ability. A study of large groups of health workers (32-62) years of age found that those with higher BMI values had lower vocabulary learning and selective attention scores, and higher 5-year cognitive decline data. Another study of cross-sections of the brain in the (54-81) year-old adult population found that a larger waist circumference resulted in higher blood pressure, which in turn reduced performance. In addition, those with low hand dexterity and low speed scores were also directly associated with higher BMI data (27). From this perspective, in healthy elderly people, obesity is negatively correlated with cognitive function, and the decline in cognitive function is most likely related to blood pressure levels.

Neuroimaging studies have also shown a link between obesity and brain abnormalities. Common brain structural abnormalities include reduced volume of the hippocampus and total parenchyma tissue, increased white matter superstrength, and temporal lobe atrophy. Studies have found that as body mass index increases in middle-aged subjects, levels of neuron survival and membrane metabolism markers (respectively N-acetylaspartic acid and choline metabolites) decrease; obvious abnormalities are usually appears in the frontal lobe.

**Sleep Disorders and Alzheimer’s Disease**

A group of studies on sleep and AD have shown that lack of sleep increases the risk of AD, especially deep sleep deficiency (28). This association has been confirmed by many epidemiological studies. Because the brain lacks a lymphatic system to clean up trash, another system is needed to clean up trash, and cerebrospinal fluid is a cleaner of brain trash (29). Deep sleep is the best time to clean up brain waste. During deep sleep, the cerebrospinal fluid cleaning waste starts a high-speed operation mode, and the brain’s glial cell volume is reduced by 60%. There is mainly a type of beta amyloid plaque deposition in brain waste, which causes neurological symptoms, including memory impairment, cognitive impairment, language dysfunction, spatial visual dysfunction, and emotional disorders. A large number of clinical cases that almost all patients with AD had found Aβ deposits in the brain tissues as early as two decades ago, of which could be adjustable by diet and moderate exercise (30).

**IMPACT OF POOR LIFESTYLE ON ALZHEIMER’S DISEASE**

**Effects of Nutritional Dietary Factors on Alzheimer’s Disease**

Dietary factors are directly related to brain aging and cognitive dysfunction. Recently, epidemiological studies have begun to analyze the effects of various dietary patterns rather than single nutrition. Dietary factors that reduce the risk of diabetes and cardiovascular disease can also reduce the risk of cognitive decline and dementia (31).

Numerous studies have shown that saturated fat intake is associated with decreased cognitive ability and increased dementia, of which w-3 fatty acids play an important role in reducing risk (32). If there is only one isolated beneficial habit (such as increasing intake of w-3 fatty acids or fruits / vegetables), it is not enough to prevent dementia. However, if you have two or more good eating habits, the risk of developing dementia is significantly reduced. Regular consumption of fruits and vegetables, fish, and w-3 rich cooking oils can reduce
the risk of AD, especially among non-carriers of ApoEε4 (33). The intake of saturated and anti-unsaturated fats may also be positively correlated with the risk of AD, but the intake of w-6 polyunsaturated and monounsaturated fats is negatively correlated with the risk (34).

In addition, diets high in saturated fats and trans-fats will lower serum cholesterol levels, which in turn will increase LDL and lower HDL. If blood cholesterol levels are high during middle age, the risk of developing AD in the later years may triple.

The benefits of fruits and vegetables are thought to come from various antioxidants and bioactive ingredients (including vitamins E and C, carotenoids, flavonoids and other polyphenols, etc.). Some animal studies have found that vitamin E and other antioxidant nutrients can reduce oxidative and inflammatory damage; however, the effects of food-based vitamin E and C intake on humans are inconsistent (35). Polyphenols can be subdivided into more than 10 groups based on their chemical structure, and about 60,000 flavonoid members have been identified (including resveratrol found in red wine and catechins found in green tea). In addition to its antioxidant properties, dietary polyphenols have significant neuroprotective effects. Also in rat experiments, blueberry extract has been shown to prevent or even reverse age-related neural signaling and cognitive deficits (36).

Studies have shown that when plasma homocysteine levels are higher than 14 mM, the risk of developing Alzheimer’s almost doubles. A 3-year trial of 818 participants found that compared with placebo, the concentration of folic acid in the serum of those taking folic acid increased by 576% and the concentration of homocysteine decreased by 26%; 3 a Folic acid supplementation significantly improved cognitive function that originally decreased with age.

In addition, dietary patterns, rather than single nutrients, have a significant impact on various health issues. There is a special type of diet called the Mediterranean diet (MeDi for short), which usually consumes high levels of vegetables, beans, fruits, fish, nuts, cereals and unsaturated fatty acids, low saturated fats and meats, low to moderate Dairy products, regular moderate drinking (mainly wine) are characterized. Studies have shown that a four-year Mediterranean diet can reduce the risk of dementia by more than a third.

The study found that the nutritional risk and incidence of malnutrition are higher in hospitalized patients with AD, the nutritional support rate is lower, and there are greater risks.

With the aging of the population, the incidence of AD has increased year by year, and the prevention and treatment of cognitive dysfunction caused by nutritional factors has drawn great attention. The in-depth study of the relationship between nutrition and AD has important social significance for reducing AD.

Effects of Drinking and Smoking on Alzheimer’s Disease

Mild to moderate drinking can prevent dementia, although alcoholism and alcoholism can cause cognitive impairment and dementia. The risk of dementia from mild to moderate alcohol consumption is significantly reduced; elderly people who regularly drink (1 to 6) glasses of beer, wine, or liquor every week regularly have a lower risk of dementia (37). Evidence suggests that limited drinking in earlier adult life may play a protective role in the risk of dementia in old age. The exact mechanism by which a small amount of alcohol may have a protective effect has not yet been established, although the health benefits of red wine are mostly thought to be caused by the polyphenol resveratrol. Ethanol is also considered to be a regulator of fatty acid metabolism, especially to promote high levels of long-chain w-3 fatty acids. A study of more than 550 women over the age of 70 showed that smoking habits were not a significant risk factor for cognitive decline or physical decline (38). Smoking can greatly increase the risk of mental aging, especially the psychological, mental and neurological disorders of old age. Studies have found that compared with people who drink moderately without smoking, alcoholics have a 36% decrease in cognitive ability. In the past, smoking was thought to have some benefit in improving cognitive decline, which may be due to the neuroprotective effects of nicotine receptor agonists.

**IMPACT OF VARIOUS SOCIAL FACTORS ON ALZHEIMER’S DISEASE**

Effects of Psychological Stress on Alzheimer’s Disease

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In the decline of cognitive ability, the role of social psychological burden is little known, and the influence mechanism is complicated. It is generally believed that the early history of depression is more or less related to the later development of dementia (40). Studies have found that psychological pain can increase the risk of memory decline. A key explanatory mechanism may involve the hypothalamus-pituitary-adrenal axis (also known as the "pressure circuit"), which links depression and anxiety to a cascade process that includes the hypothalamus and pituitary gland, because Corticotropin-releasing hormone (CRH), adrenocortical hormone (ACTH), and adrenals. Further research has shown that these hormones increase blood pressure, heart rate and blood glucose levels (41).

In addition, depression and pain can cause structural changes in the hippocampus, which can lead to memory and learning problems. Data from Alzheimer’s model mice supporting this hypothesis show that, through the use of corticotropin-releasing hormone as a mediator, isolation stress increases the level of β-amyloid in the interstitial fluid of the brain by 84%. At the same time, isolation stress can also lead to memory impairment, reduced neurogenesis, and reduced age-related proinflammatory cytokine synthesis.

Effects of Exercise and Education on Alzheimer’s Disease

More and more research shows that physical activity in old age is beneficial to improve cognitive function of the elderly. Relevant benefits include increased brain reserve and maintenance of cognitive function, as well as preventing or delaying the progression of neurodegenerative diseases such as AD. However, only a few related studies have proven that this is due to the subject’s aerobic exercise. Aerobic and resistance training increases the gray and white matter volume of the prefrontal cortex and enhances the function of critical pathways in the executive network. A randomized controlled trial shows that aerobic training has a positive effect on hippocampal volume in patients with mild cognitive impairment, mainly because aerobic training may increase hippocampal volume by increasing brain-derived neurotrophic factor levels, thereby stimulating nerves Newborn and increased complexity of dendritic networks (42).

Epidemiological data on the protective role of education in the life cycle indicates that the prevalence or incidence is lower in older populations with higher education levels. Researchers have found significant positive correlations between education and brain gray matter volume, education, and functional connectivity, suggesting that biological matrices are intrinsically related to mental functioning (43).

The Impact of Socioeconomic Status on Alzheimer’s Disease

Many findings support a strong link between the socioeconomic status of early life and the risk of later dementia. In general, in many regions, low socioeconomic status leads to increased morbidity and mortality (44); low-income populations have less access to health care and more often engage in unhealthy behaviors (such as smoking, eating unhealthy diet, alcoholism, lack of exercise, etc.) (45).

Studies have shown that there is a link between women leaving full-time education at a young age and dementia death, but men are not. However, like men and women, there is a correlation between lower household disposable income levels and absolute (1 to 5) years of high mortality at any age (46).

CONCLUSION

The pathogenesis of AD is the progressive degradation of cholinergic neurons, especially in the hippocampus and cortex, causing symptoms such as memory loss, impaired judgment, and depression; its pathological characteristics are: Aβ in cells External accumulation (senile plaques) and neurofibrillary tangles (47).

In the past ten years, studies have shown that biological and sociological factors have a significant effect on the development of AD. Various genetic factors, numerous environmental dangers, overweight and obesity, sleep disorders, nutrition and diet, drinking and smoking, psychological stress and depression, economic status, etc., comprehensively regulate the cognitive function of the public. The three major genetic markers of AD, including APP, PSEN1, and PSEN2, are known to be associated with increased Aβ production, eventually leading to neuronal death and dementia. APOE has been recognized as a major genetic marker for late-onset AD. With the development of biological sciences, the development
of advanced computing and systems biology tools to analyze big data will help neuroscientists to conduct more in-depth research on the etiology of AD and prevent the occurrence of AD (48).

Lifestyle as a risk factor for AD can be intervened early. The cognitive aging hypothesis that "use leads to progress, and waste leads to regression" indicates that more participation in physical, social, and intellectual activities in later life can combine different environments to enhance the slowing effect on functional and cognitive decline. Some adult subjects who participate in various activities perform better, and it can be predicted that they will gradually reduce cognitive impairment over time, and the likelihood of developing AD will decrease in the future (49). As mentioned earlier, people protect Alzheimer’s from health habits (mild to moderate drinking, dietary antioxidants, Mediterranean diet, controlled physical activity, occupational exposure, social, emotional support and continued learning, etc.) A broad consensus has been formed on the role, which will help to further establish a cognitive protection structure. Although many controllable factors can reduce the risk of AD in old age, there are still many uncertainties about the direct impact mechanism of these activities in old age, and everyone needs to work together to solve it (50).

**ARTICLE INFORMATION**

**Author Affiliations:** Intelligence Brain Institute, Carson City, NV 89701, USA. (Trepson).

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