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Alzheimer Hastalığında Risk Faktörlerinin ve Beslenme Yaklaşımlarının Potansiyel Rolü: Ketojenik Diyet Üzerine Bir İnceleme Çalışması

The Potential Role of Risk Factors and Nutritional Approaches in Alzheimer's Disease: A Review Study on the Ketogenic Diet

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ÖZ

Demans türleri arasında en sık görülen formu olan Alzheimer hastalığının yaşlanmaya bağlı olarak prevalansı dünya genelinde hızla artmaktadır. Bireylerin günlük yaşam kalitesinde düşüşe ve bilişsel fonksiyonlarında kayba neden olan, günümüzde önde gelen ciddi sağlık sorunlarından biri olarak yer almaktadır. Alzheimer'ın patogenezinde beyin-enerji üretim sürecinde ortaya çıkan glikoz metabolizması bozuklukları temel bir etkiye sahiptir. Alzheimer hastalığında, GLUT-1 proteinlerinin ekspresyonunda azalma veya fonksiyonlarındaki bozulma, nöronların glikoz alımını sınırlamakta, enerji eksikliğine ve sinaptik disfonksiyona neden olmaktadır. Bu durum beta amiloid birikmesine ve tau mekanizmasındaki bozulmasına neden olarak Alzheimer'ın hızla ilerlemesine yol açmaktadır. Bu bağlamda alternatif enerji kaynağı sunabilen ketojenik diyetin potansiyel önemi ortaya çıkmaktadır. Günümüzde henüz Alzheimer hastalığının kesin ve onaylanmış bir tedavisi bulunmamakla berber değiştirilebilir risk faktörlerine yönelik yaklaşımların hastalığın seyrini yavaşlatma potansiyeline sahip olduğu düşünülmektedir. Bu derlemede bireyin yaşam biçimi ve özellikle beslenme alışkanlıklarının Alzheimer hastalığının gelişimindeki potansiyel etkileri ele alınacak; ayrıca ketojenik beslenmenin beyin-enerji metabolizması ve bilişsel işleyiş üzerindeki olası etkileri nedeniyle Alzheimer hastalığı üzerindeki rolü incelenecektir.

Anahtar Kelimeler: alzheimer hastalığı, risk faktörleri, beslenme yaklaşımları, ketojenik diyet

ABSTRACT

Alzheimer's disease (AD), the most common form of dementia, is rapidly increasing in prevalence worldwide due to aging. It is one of the leading serious health problems today, causing a decrease in the quality of life and loss of cognitive function. Impairments in glucose metabolism, which occur in the brain's energy production process, play a key role in the pathogenesis of Alzheimer's. In Alzheimer's disease, decreased expression or impaired function of GLUT-1 proteins limits neurons glucose uptake, leading to energy deficiency and synaptic dysfunction. This leads to beta amyloid accumulation and disruption of the tau mechanism, leading to the rapid progression of Alzheimer's. In this context, the potential importance of the ketogenic diet, which can provide an alternative energy source, emerges. While there is currently no definitive and approved treatment for Alzheimer's disease, approaches targeting modifiable risk factors are thought to have the potetial to slow the course of the disease. This review will address the potential effects of an individual's lifestyle, and particularly their eating habits, on the development of Alzheimer's disease. Additionally, the role of ketogenic nutrition in Alzheimer's disease will be examined due to its possible effects on brain-energy metabolism and cognitive functioning.

Keywords: alzheimer's disease, risk factors, nutritional approaches, ketogenic diet

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INTRODUCTION

Alzheimer's disease (AD) is a neurodegenerative disease that leads to cognitive loss and irreversible damage to central nervous system tissues due to the progression of degenerative processes in neurons (1). AD reduces the individual's ability to live independently as a result of deterioration in cognitive and functional capacity and causes a significant decrease in quality of life (2). Additionally, the disease can adversely affect social interaction and adaptation to the environment, thereby increasing premature mortality risk. It is believed that controlling modifiable risk factors for Alzheimer's disease, while not preventing the disease entirely, may contribute to slowing its progression. In this context, an individual's lifestyle and particularly their dietary habits, is of great importance. The ketogenic diet has recently gained increasing importance due to its potential impact on the course of Alzheimer's disease. In this review, the modifiable risk factors of Alzheimer's disease are discussed. Additionally, the effects of selected dietary components, particularly the ketogenic diet, on the development and progression of the disease are examined. The aim of this review is to summarize these modifiable risk factors and evaluate the potential impact of the ketogenic diet on Alzheimer's disease based on current scientific evidence.

Pathogenesis of Alzheimer's Disease

In patients with Alzheimer's disease, beta-amyloid (Aβ) peptides are generated through the cleavage of the amyloid precursor protein. The abnormal accumulation of beta-amyloid protein and phosphorylated tau (pTau) in the body, particularly affecting glucose transporters, leads to severe damage to the blood-brain barrier and mitochondrial dysfunction (3). In Alzheimer's disease, disturbances in glucose metabolism and the resulting mitochondrial dysfunction lead to an energy imbalance. This energy deficiency is most pronounced in the hippocampus, while other brain regions are also affected, which leads to cognitive decline (4).

A study of families with early-onset Alzheimer's disease identified three key genetic mutations implicated in the development of the disorder. These mutations are in the APP gene (amyloid precursor protein) located on chromosome 21, the PSEN1 (Presenilin1) gene located on chromosome 14, and the PSEN2 (Presenilin2) gene located on chromosome 1. Alterations in these genes are considered to play a pivotal role in the hereditary transmission of Alzheimer's disease. Mutations in the genes encoding these three transmembrane proteins disrupt amyloid-β metabolism, accelerate pathological processes, and usually lead to the onset of the disease before the age of 60 (5,6).

In cases of late-onset Alzheimer's disease, a mutation in the APOE ε4 allele (apolipoprotein E) has been identified as a significant risk factor for the development of the disease across different populations. The APOE gene encodes a serum protein involved in cholesterol metabolism and exists in three different allelic forms. While the E4 allele is found in approximately 20% of healthy individuals, its frequency has been reported to double to around 40% in patients with Alzheimer's disease (5,6). Considering the presence of these risk alleles in an individual's genome, a 75–85% accurate association can be established in patients with Alzheimer's disease (3,6,7).

Seven modifiable risk factors have been identified for Alzheimer's disease. These include diabetes, midlife hypertension, obesity, smoking, depression, cognitive inactivity, and physical inactivity. It has been estimated that if a 10% reduction in each of the seven risk factors is achieved, the number of Alzheimer's cases worldwide could decrease by approximately 1.1 million. If the incidence of these risk factors falls below 25%, the number of cases could decrease by approximately 3 million (8).

Diabetes: In the pathogenesis of Alzheimer's disease, disturbances in glucose metabolism interact with structural and functional lesions in brain tissue, playing a central role in disease development. Insulin signaling pathways are affected in Alzheimer's disease. Hyperglycemia, insulin resistance, and associated inflammation resulting from diabetes disrupt the production and clearance mechanisms of beta-amyloid, leading to its accumulation in the brain. Increased amyloid burden damages neurons, disrupts synaptic function, and contributes to cognitive decline. This mechanism can be partially considered as a reflection of insulin resistance (9). In a study conducted by Lu et al., the relationship between diabetes and dementia, including Alzheimer's disease, was examined. Two of eight prospective studies found a statistically significant increase in the risk of Alzheimer's disease in patients with diabetes (10). In a separate study conducted by Profeno et al., the relationship between diabetes and dementia was examined across nine prospective studies. Six of these studies were consistent with the results obtained by Lu et al. (11).

Smoking: One of the most common causes of the high global incidence of Alzheimer's disease has been linked to smoking. The relationship between smoking and AD is primarily mediated by disorders of the cardiovascular system, particularly atherosclerosis and cerebrovascular diseases. Additionally, due to the numerous neurotoxins present in tobacco smoke, it contributes to increased oxidative stress, inflammation, and other mechanisms, collectively leading to a heightened risk of Alzheimer's disease (12).

Physical Inactivity: Physical inactivity is associated with an increase in various cardiovascular risk factors, particularly diabetes, hypertension, and obesity. Consequently, it is linked to an elevated risk of dementia and, therefore, Alzheimer's disease (8). Regular physical activity in midlife has been shown to significantly reduce the risk of developing Alzheimer's disease and other forms of dementia in later life, even among individuals carrying the APOE ε4 allele (13). One study found that participants who engaged in more frequent weekly exercise and performance-based physical activity had a statistically significant lower risk of developing Alzheimer's disease (14). It is also suggested that physical activity is associated with cognitive functions and may help reduce the risk of developing Alzheimer's disease (8).

Cognitive Inactivity: Maintaining cognitive abilities such as thinking, learning, and problem-solving is crucial for brain function. These abilities have been associated with a reduced risk of developing dementia and Alzheimer's disease (15). Recent neuroimaging studies have revealed that lifelong engagement in cognitive and complex activities may exert a protective effect on hippocampal structure. Intense mental activity has been shown to reduce age-related hippocampal atrophy, protect against neurodegenerative diseases, and support cognitive reserve. Cognitively stimulating activities have been observed to reduce the risk of developing Alzheimer's disease and other types of dementia by supporting hippocampal volume and functional integrity throughout life (15,16,17).

Depression: Depression and decreased levels of neuronal growth factors are seen in patients with Alzheimer's disease and other dementias. This negatively impacts the survival and repair capacity of neurons, leading to cognitive impairment. This condition has been associated with neuronal loss and memory impairment, particularly in the hippocampal region. In depression, reduced levels of neuronal growth factors may contribute to an increased risk of Alzheimer's disease (18). An analysis of 13 studies found that individuals with a history of depression had approximately twice the risk of developing dementia compared to those without such a history (19).

Hypertension-Hypotension: Hypertension in midlife has been consistently associated with an increased risk of dementia and Alzheimer's disease in later life. Four out of five studies reported this association as statistically significant (8). Studies have also shown that low blood pressure (below 70 mmHg) may increase the risk of dementia and Alzheimer's disease in individuals aged 65 and older (20). Antihypertensive treatment provides a protective effect against dementia and Alzheimer's disease by slowing the progression of atherosclerosis, limiting lesion formation, and improving cerebral perfusion. Studies have shown that antihypertensive medication use plays a protective role against the development of dementia and Alzheimer's disease (16,21).

Obesity: Most studies have reported that a higher body mass index (BMI) increases the risk of all-cause dementia, with the results being statistically significant (11,22). Alterations in adipose tissue metabolism may lead to insulin resistance and hyperinsulinemia, which can impair amyloid clearance in the brain (23).

The impact of eliminating all these factors on the incidence of AD has not been definitively established. Moreover, many of these risk factors are interconnected, as hypertension, diabetes, and obesity frequently coexist and collectively influence physical activity levels (8).

The Role of Nutrition on Alzheimer's Disease

In addition to the seven identified modifiable risk factors for Alzheimer's disease, studies have suggested that dietary habits may also be associated with disease risk. According to data from a nearly four-year study by Morris et al., increased intake of saturated fats was associated with a 70% higher risk of developing Alzheimer's disease. The study further indicated that the consumption of saturated fats and trans-unsaturated fatty acids may be associated with an increased risk of developing the disease. Supporting this view, another study reported that increased fish consumption reduces the risk of developing Alzheimer's disease. Participants who consumed fish weekly had a 60% lower risk compared to those who rarely consumed it. Overall, these findings suggest that increased intake of monounsaturated, omega-3, and polyunsaturated fats may have a protective effect in reducing the risk of Alzheimer's disease. This highlights the potential role of dietary fat composition in modulating disease risk (24).

Resveratrol, a potent antioxidant, has been suggested to be an important compound in the prevention and treatment of Alzheimer's disease, due to its ability to inhibit amyloid-beta peptide formation and suppress pro-inflammatory cytokines (4). A study supporting this hypothesis was conducted by Lindsay and colleagues. This study reported that wine consumption reduced the risk of Alzheimer's disease by approximately 50%. Similarly, the same research indicated that moderate coffee consumption was associated with a 65–70% reduction in dementia risk and a 62–64% reduction in Alzheimer's disease risk (25).

Another study found that consuming three or more fruits per day reduced the risk of developing Alzheimer's by approximately 60% (26). In a study conducted by Devore et al. among older adults in the Netherlands, it was determined that vitamin E was the only antioxidant among beta-carotene, flavonoids, and vitamins C and E that contributed to a reduction in the risk of Alzheimer's disease (27). A Chicago-based study involving 6,158 individuals aged 65 and older determined that dietary intake of niacin (vitamin B3) may confer protection against the risk of Alzheimer's disease. Participants in the highest quintile of niacin consumption exhibited an approximately 80% reduction in the risk of developing Alzheimer's disease (28). Of the 64 studies reviewed, 50 revealed a significant association between AD and diet (29).

Ketogenic Diet

The ketogenic diet is a nutritional model in which a large proportion of energy is derived from fats. Protein intake is maintained at adequate levels for growth and tissue repair. The ketogenic diet is a nutritional model in which carbohydrate intake is restricted to less than 10% of total energy. It is generally limited to approximately 50 grams per day (30). As a result of limited carbohydrate intake, the body begins to utilize ketone bodies for energy production. In the planning of a ketogenic diet, macronutrient requirements should be considered. Moreover, attention must be given to ensuring adequate intake of essential vitamins and minerals (31).

Regular monitoring is crucial when implementing a ketogenic diet. Patients should undergo evaluation for ketonuria and ketonemia at three-month intervals. With these tests metabolic status as well as dietary compliance should also be monitored. The diet is generally initiated with a 12–48 hour fast, and blood beta-hydroxybutyrate levels are monitored to confirm the onset of ketosis. Levels of 2–5 mmol/L at the end of the first week indicate that ketosis is continuing appropriately (32).

The Relationship between Alzheimer's Disease and Ketogenic Diet

The brain can meet its energy needs through both glucose and ketone bodies. However, when glucose and ketones coexist, ketone bodies have been shown to be preferentially utilized because ketone bodies cause less oxidative damage than glucose and are regarded as a more reliable and efficient energy source for the brain. Some studies emphasize that the brain can effectively utilize ketone bodies regardless of age. This function persists at similar levels across all age groups without decline. Furthermore, ketone bodies have been shown to continue serving as an efficient energy source for the brain even when glucose is insufficient for energy production (33).

In Alzheimer's disease, the development of insulin resistance in the brain leads to impaired glucose metabolism, which in turn causes an energy deficit. There is a potential for this energy deficit to be compensated through ketone bodies. This situation enables the ketogenic diet to be considered as a supportive approach in Alzheimer's disease. In her book The Complete Guide to Ketones, Dr. Mary Newport also states that the ketogenic diet significantly improves Alzheimer's symptoms by directly increasing ketosis in the body (34).

Some animal studies have demonstrated that levels of amyloid plaques characteristic of Alzheimer's disease can be reduced through a ketogenic diet. Furthermore, ketone bodies have been suggested to play a role in reducing inflammation, potentially preventing or slowing cognitive decline over time. Ketone bodies have also been shown to enhance anti-inflammatory pathways that protect against amyloid plaque pathology by regulating neuroinflammation (34).

Experimental Studies on Alzheimer's Disease and the Ketogenic Diet

In a New Zealand–based study conducted in 2021, 26 patients with Alzheimer's disease were placed on a modified ketogenic diet for 12 weeks. The findings indicated that patients with Alzheimer's disease on a ketogenic diet experienced a significant improvement in daily quality of life compared to those following a low-fat diet. Cardiovascular risk factors were generally found to show favorable changes, and the adverse effects of the ketogenic diet were observed to be limited. The study suggests the potential applicability of ketogenic nutrition in patients with Alzheimer's disease but emphasizes that further research is needed to clarify its outcomes (35).

In a study conducted by Krikorian et al., the relationship between ketone levels and memory performance in older adults placed on a very low-carbohydrate diet for six weeks was examined (36). Additionally, in a study conducted by Forsythe et al., the relationship between very low-carbohydrate diets and inflammatory factors associated with neurodegeneration was examined (37). In a different clinical study, improvements in memory were observed following the implementation of a ketogenic or very low-carbohydrate diet. In another case study, the administration of oral ketone or monoester ketogenic agents was associated with benefits in cognitive performance, mood, emotional state, and self-care (32).

In a study conducted by Taylor and colleagues, ten patients diagnosed with mild Alzheimer's disease were placed on a ketogenic diet consisting of 70% fat for three months. Initially, approximately 10% of their energy intake was derived from MCT oils (medium- chain triglycerides) and this proportion increased over time. At the end of the study, improvements were observed in tests assessing memory and attention performance. These findings suggest that ketosis-inducing diets may exert beneficial effects on memory and other cognitive functions (31,34).

In a study conducted by Ota and colleagues, 20 patients over the age of 70 diagnosed with Alzheimer's disease were administered formulations containing 50 grams of MCT daily for 12 weeks. The study found that, compared to the control group, participants receiving MCT supplementation scored significantly higher on the Wechsler–Adult Intelligence Scale–Third Edition (WAIS-III) and Memory Scale. The findings indicate that MCT supplementation, added to a regular diet, increased blood ketone levels and had beneficial effects on cognitive performance in patients with Alzheimer's disease. However, the study noted that, due to the lack of assessment of short-term effects and the limited sample size, further research with larger cohorts is needed (38). Several studies have shown that MCT and ketone supplementation can improve cognitive performance (38).

Another study observed that administering a ketogenic diet for four months to 7-month-old 5XFAD mice diagnosed with Alzheimer's disease resulted in statistically significant improvements in learning, memory, and working memory. These cognitive enhancements were associated with the restoration of synaptic density in the hippocampus and cortex. Furthermore, it has been observed that a ketogenic dietary regimen mitigates neuroinflammation by limiting amyloid plaque accumulation. The findings indicate that the pathological progression of Alzheimer's disease can be suppressed through a ketogenic diet, suggesting its potential therapeutic effect in the management of Alzheimer's disease. However, the study also noted that initiating the ketogenic diet after the ninth month did not confer any observable benefits. These findings suggest that dietary interventions initiated at an earlier stage may potentially be more effective. Moreover, it has been observed that shorter-term implementation of the ketogenic diet produces more limited effects. Collectively, these results indicate that the timing of initiation and duration of the ketogenic diet may play a critical role in modulating Alzheimer's disease pathophysiology (39).

In a study conducted by Henderson et al., the relationship between an individual's ApoE4 genotype and the response to a ketogenic diet was examined. The study included individuals with mild to moderate Alzheimer's disease who were ApoE4-negative and received medium-chain triglyceride (MCT) supplementation. Participants were administered 10 g of MCT during the first seven days, followed by 20 g from day eight to day ninety. As a result of the intervention, an increase in serum ketone body concentrations was observed, accompanied by improvements in cognitive function (39, 40).

A diet with a high glycemic index has been associated with increased insulin resistance and a higher risk of developing Alzheimer's disease (41)

The findings from these studies indicate that the ketogenic diet may exert potential beneficial effects on brain function and cognitive performance, as well as positively influence neurodegenerative processes. However, comprehensive, high-quality studies are needed to definitively assess these effects. Various studies in the literature have evaluated the effects of ketogenic diet interventions in patients with Alzheimer's disease.

The general characteristics of these studies are discussed in the text, while the key findings are summarized in Table 1.

Side Effects of the Ketogenic Diet

A study conducted by Xu et al. examined the side effects of the ketogenic diet in patients with Alzheimer's disease. Approximately 20% of the participants experienced gastrointestinal symptoms such as diarrhea and constipation following the diet; however, these symptoms were temporary and resolved over time (41). Adequate fluid intake and the consumption of fiber-rich foods can help manage these issues, while hydration requires careful monitoring due to the particular risks it may pose for elderly individuals. Moreover, during the early stages of ketogenic diet implementation, side effects such as nausea, vomiting, acidosis, hypoglycemia, hypercalciuria, hypocalcemia, and hypertriglyceridemia have been reported (42).

Table 1.The key findings of selected studies on ketogenic diet interventions in Alzheimer's disease are summarized in Table 1

Author(s) & years	Location	Study Type	Population	İntervention	Main findings
Phillips, M. C. et. al. August, 2018-2021	Conducted at Waikato Hospital, a tertiary center in Hamilton, New Zealand.	A single-phase two-period randomized crossover trial	Randomized 26 patients,	12 week modified ketogenic diet hospital clinic of AD patients.	In this study, the ketogenic diet led to notable improvements in the daily living quality of Alzheimer's patients, with limited adverse effects observed.
Krikorian et al. July 2010	Cincinnati, Ohio, USA	Not reported	Randomized 23 older adults patient (10 men, 13 women)	6-week intervention period	The findings indicate that, even in the short term, very low carbohydrate intake may improve memory function in older adults at increased risk of Alzheimer's disease.
Forsythe et al. 2018	Sherbrooke, Quebec, Canada	Blinded randomized controlled trial	52 patients with mild cognitive impairment	30g of MCT taken daily for 6 months	An increase in brain ketone uptake was found to be positively associated with various cognitive measures.
Taylor et. al. December 2013–July 2016	University of Kansas Alzheimer's Disease Center, Lawrence, Kansas, USA	Single-arm pilot clinical trial	15 participants with AD.	MCT supplemented ketogenic diet for 3 months, followed by a normal diet for 1 month	Due to the small sample size, interpretation of cognitive performance data is limited; however, a statistically significant improvement was observed.
Ota et. al. 2018	National Center of Neurology and Psychiatry, Japan. Tokyo- Japan	A double-blind placebo-controlled study with	Studied 20 patients 11 males, 9 females; mean age 73.4 ± 6.0 years) diagnosed with AD.	Each patient was given 50 g of a ketogenic formula containing 20 g of MCTs per day in addition to their normal diet. Cognitive functions were tested at weeks 4, 8, and 12.	In this study, no acute cognitive effects of the ketogenic formula were observed; however, its 2–3 month use was reported to have beneficial effects in patients with mild-to-moderate Alzheimer's disease. Due to the small sample size, the results should be interpreted with caution.
XU, Yunlong, et al. 2021	Shenzhen, China	Preclinical in vivo experimental study (5xFAD transgenic mouse model)	The male 5xFAD mice were fed a ketogenic diet from 7 to 11 months of age	4 months of ketogenic diet	In this experiment conducted on rats, improvements in cognitive function were observed; however, the effects of short-term ketogenic diet were limited. No cognitive effects were reported when the ketogenic diet was initiated in the late stages of Alzheimer's disease.

The high fat content of the ketogenic diet may affect the liver and kidneys. However, a study by Murugan and Boison reported that the ketogenic diet did not significantly impair liver function (43). To ensure safe implementation, periodic monitoring through laboratory tests is recommended. Furthermore, because of the potential for increased side effects when the ketogenic diet is combined with pharmacological treatment, its implementation under clinical supervision is advised (41).

In the ketogenic diet model, carbohydrate intake is minimized while fat consumption as an energy source is increased. According to Ruiz Herrero and colleagues, this approach increases the risk of vitamin and mineral deficiencies, and restriction of selected foods brings about nutritional inadequacy. Therefore, the nutritional status of patients on a ketogenic diet should be closely monitored, and appropriate supplementation provided when necessary (42).

The implementation of a ketogenic diet in elderly patients with Alzheimer's disease involves restrictions in food selection. Combined with the effects of the disease, this can create a psychological burden for the individual. This situation may not only hinder adherence to the diet but also increase the tendency of the disease to affect nutritional intake (31).

Long-term use of the ketogenic diet has been reported to increase proteinuria, hyperuricemia, metabolic acidosis, aminotransferase levels, and the risk of urinary tract stones. Serious complications may particularly occur in elderly individuals with comorbidities. Therefore, the routine use of the ketogenic diet in Alzheimer's disease should be carefully considered. The diet has been suggested to play a supportive role in the treatment of neurodegenerative diseases, although further studies are required to better understand its effects (42).

RESULTS AND DISCUSSION

Alzheimer's disease is becoming increasingly prevalent with the aging population, posing significant health challenges. Therefore, scientific studies on strategies to alleviate its symptoms may therefore make important contributions to the development of approaches aimed at slowing its progression and preventing its onset. The ketogenic diet, as one of these approaches, has emerged as a supportive nutritional intervention for neurodegenerative diseases. Studies indicate that ketogenic nutrition may have potential effects on cognitive functions and can lead to significant improvements in patients' quality of life. Similar benefits have also been reported with the use of ketogenic agents in combination with a balanced diet. Accordingly, the ketogenic diet may provide potential benefits for patients with Alzheimer's. However, further studies are needed to establish more conclusive results. Despite these promising findings, current evidence remains insufficient to recommend ketogenic diet therapy as a standard treatment in clinical practice. Even if modifiable risk factors, including diet, are controlled as much as possible, the presence of non-modifiable genetic risk factors currently makes complete prevention of Alzheimer's disease impossible.

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