BOGUCKA, Adrianna, KOTKOWIAK, Agata, KNYCHALSKA, Karolina, ŁABUDA, Mikołaj, SOWIŃSKA, Teresa, SZEMA, Agnieszka, MENTEL, Oliwia, SŁOJEWSKA, Aleksandra, SIKORA, Jakub and KRÓLIKOWSKA, Klaudia. The Role of Diet, Physical Activity, and Lifestyle in Alzheimer's Disease Prevention: A Literature Review. Journal of Education, Health and Sport. 2025;80:60011. eISSN 2391-8306.
https://doi.org/10.12775/JEHS.2025.80.60011
https://apcz.umk.pl/JEHS/article/view/60011

The journal has had 40 points in Minister of Science and Higher Education of Poland parametric evaluation. Annex to the announcement of the Minister of Education and Science of 05.01.2024 No. 32318. Has a Journal's Unique Identifier: 201159. Scientific disciplines assigned: Physical culture sciences (Field of medical and health sciences); Health Sciences (Field of medical and health sciences).
Punkty Ministerialne 40 punktów. Załącznik do komunikatu Ministra Nauki i Szkolnictwa Wyższego z dnia 05.01.2024 Lp. 32318. Posiada Unikatowy Identyfikator Czasopisma: 201159. Przypisane dyscypliny naukowe: Nauki o kulturze fizycznej (Dziedzina nauk medycznych i nauk o zdrowiu); Nauki o zdrowiu (Dziedzina nauk medycznych i nauk o zdrowiu).
The authors declare that there is no conflict of interests regarding the publication of this paper.
Received: 02.04.2025. Revised: 06.05.2025. Accepted: 06.05.2025. Published: 09.05.2025.

The Role of Diet, Physical Activity, and Lifestyle in Alzheimer's Disease Prevention: A Literature Review

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ABSTRACT

Introduction and Purpose:

Alzheimer's disease is currently the most common cause of dementia worldwide, primarily affecting older individuals. By impairing cognitive abilities, it significantly diminishes the quality of life of patients. Predictions indicate that its incidence will rise dynamically over the coming years due to population aging. To date, no treatment has been developed that addresses the underlying causes. As a result, increasing attention has been given to identifying factors that could prevent the development of the disease. This paper examines the literature analyzing the impact of lifestyle, diet, and physical activity on the prevention of Alzheimer's disease.

State of Knowledge:

Positive lifestyle factors that have been repeatedly analyzed for their preventive value include, among others: a high level of education, engagement in pro-cognitive activities, social bonding, a healthy diet, and physical activity exceeding 150 minutes per week. All of the above have shown correlations with a lower incidence of Alzheimer's disease, although not all researchers are certain about the positive impact of physical activity. Notably, higher education and its associated cognitive reserve theory, as well as the impact of the MIND and Mediterranean diets

on inhibiting the inflammatory process, stand out. Currently, loneliness, smoking, obesity, diabetes, and hypertension may account for up to half of Alzheimer's cases.

Conclusion:

Focusing on a single element influencing the development of Alzheimer's disease is less important than combining multiple factors, such as an appropriate diet, regular physical activity, and social and cognitive engagement while avoiding recognized risk factors. Only this approach may help reduce millions of cases of dementia in the future.

Keywords: Alzheimer's disease; lifestyle; Mediterranean diet; physical activity; dementia.

INTRODUCTION

Alzheimer’s disease is a neurodegenerative brain disorder responsible for 60-80% of dementia cases [2,3]. Its symptoms mainly include memory, behavioral, communication, and other cognitive function disturbances, which lead to a significant decline in quality of life [3,5].

In 2019, the global population of individuals affected by Alzheimer’s disease was approximately 57.4 million cases, and it is projected to increase to 152.8 million by 2050, representing nearly a threefold increase in incidence within just 30 years [4]. This rise in prevalence is primarily linked to the aging population, especially in developed countries like Poland. Alzheimer's disease and other dementias ranked as the 4th leading cause of death in Poland in 2019 [1].

The brain degeneration in individuals with Alzheimer's disease is caused by the accumulation of two proteins: amyloid beta (Aβ) peptide and hyperphosphorylated tau protein. These proteins form neurofibrillary tangles (NFTs) and neuritic plaques, which accumulate in neurons, glial cells, and intercellular spaces, leading to neuronal atrophy, neurotransmission disturbances, and an inflammatory response [3,6,7]. These changes begin many years before the onset of dementia, and research indicates that their presence is not necessarily indicative of cognitive impairment development [8]. The individual ability of the brain to tolerate pathological changes is the reason why accumulated proteins typically cause cognitive disturbances after the age of 65, with the risk increasing with age [3].

In elderly individuals, pathological brain changes overlap with cardiovascular changes, which may also contribute to the development of various types of dementia. However, cardiovascular disease risk factors are not directly linked to the pathophysiology of Alzheimer's disease [9,10]. Often, elderly individuals exhibit mixed dementia, resulting from concurrent vascular dementia and Alzheimer's disease [3]. Lifestyle, diet, and physical activity can influence dementia not only in the context of Alzheimer's disease but also in cardiovascular diseases.

In an era when society is aging, and this trend is expected to intensify, it is important to focus on identifying preventive factors for dementia, especially those affecting Alzheimer's disease, which, as mentioned above, is the most common cause of dementia worldwide [2,3]. This is a particularly significant issue in light of the lack of effective disease-modifying treatment for Alzheimer's disease. Current treatments still focus solely on slowing disease progression and alleviating symptoms [11]. In this review, we will focus on previous attempts to answer the question: how can Alzheimer's disease be prevented? We will address studies analyzing lifestyle, diet, and physical activity elements that may reduce the population-wide risk of developing dementia in the context of Alzheimer's disease and attempt to draw conclusions regarding their effectiveness.

DESCRIPTION OF THE STATE OF KNOWLEDGE

Lifestyle

The prevention of Alzheimer's disease through lifestyle modification encompasses many aspects: from education, social engagement, exposure to stress, and cognitive stimulation, to smoking, depression, lifestyle diseases such as hypertension, diabetes, obesity, and finally, diet and physical activity. The last two factors will be discussed separately in more detail in the following paragraphs, while this section will focus on the remaining factors mentioned.

There are numerous review articles that demonstrate that individuals who engage in cultural, social, and intellectual activities throughout their lives achieve higher scores on cognitive tests and are less likely to develop neurodegenerative disorders [12]. In 2007, a study was conducted involving 700 elderly individuals. They were observed in terms of engagement in cognitive activities, such as reading, puzzles, board games, and their influence on participants' cognitive abilities. During the study, 90 individuals developed Alzheimer's disease. It was found that

individuals with low cognitive activity had a 2.6 times higher risk of developing Alzheimer's disease compared to those with higher cognitive activity [25]. Social interactions and forming bonds are directly linked to the hormone oxytocin, which is capable of regulating depressive, anxious, and social behaviors as well as cognitive functions [26]. It has been observed that oxytocin reverses memory and learning disturbances in animal models, making it a potential target not only for prevention but also for future Alzheimer's disease therapies [27]. Studies suggest that individuals who perceive themselves as lonely have an increased risk of dementia, particularly Alzheimer's disease, but not vascular dementia [28]. However, this mainly pertains to long-term loneliness. Short-term loneliness appears to have a more protective effect against Alzheimer's disease than the absence of loneliness. This may be related to the fact that transient loneliness often results from negative life events or unexpected accidents, which help to develop psychological resilience later in life. Additionally, temporarily lonely individuals may be more likely to engage in daily activities, fostering social integration and thus benefiting cognitive abilities [29]. A higher level of education may delay the onset of Alzheimer's disease, in part due to the increase in cognitive reserve. This enables the brain to compensate for degenerative changes, making it more resistant to presenting Alzheimer's disease symptoms [30, 34]. This theory is supported by imaging studies that have shown a correlation between brain structure and education level. A higher number of years of education correlated with increased cortical thickness [32]. Furthermore, individuals with higher education levels reported the onset of symptoms earlier [31], allowing for faster intervention with treatments that slow the progression of Alzheimer's disease. However, some studies suggest that in individuals with higher education levels, when dementia symptoms appear, the disease progresses more rapidly compared to those with lower education levels [33]. This may be due to the fact that the deterioration of a patient who previously exhibited high cognitive abilities is more noticeable and contrasts sharply with their prior health condition. Another particularly important element of lifestyle, stress, significantly increases the risk of Alzheimer's disease. This occurs for several reasons. Stress chronically activates the hypothalamic-pituitary-adrenal (HPA) axis, leading to the overproduction of cortisol, which can damage the hippocampus—the brain region responsible for memory consolidation and cognitive abilities [38,40]; chronic stress can increase amyloid β production [39]; impair neuroplasticity, which is the brain's ability to form new neural connections [40]; and influence chronic inflammation [41]. One example supporting this theory is war veterans suffering from PTSD, who had twice the risk of developing dementia compared

to veterans without PTSD [35,36]. Childhood stress, such as living in an orphanage or foster care, experiencing crises, problems with teachers, school relationships, or war-related migration, can have a lasting impact on brain development and resilience to later stressors. This is supported by a 2018 study that involved 2,682 middle-aged men, who participated in health studies and interviews about their childhood experiences. The results indicated that childhood stress exposure doubled the risk of dementia among the participants [37].

This section will address factors that are more likely to increase the risk of Alzheimer's disease, but similarly, avoiding them has a protective effect. The literature indicates that smoking is associated with a significantly increased risk of Alzheimer's disease, possibly due to oxidative stress. Among the recognized modifiable risk factors, smoking, along with low education levels, has been attributed to the greatest number of Alzheimer’s disease cases [42]. Depression increases the risk of Alzheimer's disease in a similar manner to the stress discussed earlier. This risk is also influenced by accompanying sleep disturbances and anxiety [67]. A cohort study conducted among Danish citizens with depression at different ages found that depression more than doubled the risk of Alzheimer's disease, particularly when it occurred at a younge or middle age [66]. However, when depression occurs in older age, it may not serve as a risk factor, but rather as an early symptom of dementia itself, and caution should be exercised when analyzing its impact at this age [68]. Another source of pathology in Alzheimer's disease are vascular diseases and their underlying causes, such as hypertension, obesity, and diabetes. Several pathologies, such as endothelial damage, arterial stiffness, atherosclerosis, and disruption of the blood-brain barrier, can ultimately lead to brain ischemia, which in turn results in changes typical for Alzheimer's disease, such as atrophy of specific brain regions, white matter changes, and amyloid Aβ accumulation. Furthermore, chronic hypertension causes smooth muscle hypertrophy of blood vessels and is associated with increased vascular resistance, contributing to oxidative stress and inflammatory responses [69]. Systolic hypertension occurring in middle age increases the risk of Alzheimer's disease by 18% in stage 1 hypertension and 25% in stage 2 hypertension. Diastolic hypertension, however, likely has no impact on this risk [70]. Obesity, in addition to its indirect impact on the aforementioned vascular changes, can influence the development of Alzheimer's disease in many other ways. Primarily, obesity is associated with chronic localized and systemic inflammation, leading to insulin resistance and subsequent chronic hyperglycemia. In the brain, there is an increase in the concentration of tumor necrosis

factor-α (TNF-α), which can block intracellular insulin signaling by affecting the insulin receptor substrate 1 (IRS-1). Impaired insulin function likely leads to amyloid Aβ accumulation and the lack of hyperphosphorylated tau protein degeneration. Insulin resistance not only reduces brain glucose metabolism, limiting the brain's access to its primary energy source, but also promotes blood vessel constriction, causing reduced blood flow and brain atrophy [71]. Chronic hyperglycemia is reflected by increased levels of glycated hemoglobin (HbA1c). It has been shown that an HbA1c level ≥6.5% increases the risk of Alzheimer's disease by 2.8 times, and an HbA1c level ≥7% raises the risk to 4.7 times [72]. A high BMI in middle age is associated with an increased risk of Alzheimer's disease, but this relationship appears to differ in older adults, where a high BMI likely reduces the risk. Studies have shown that obese seniors had a larger hippocampal volume and less amyloid Aβ accumulation [73]. We will not discuss the pathophysiological pathway by which diabetes contributes to the development of Alzheimer's disease, as it is similar to the pathway related to obesity. We would just like to mention that a large cohort study involving over a million participants demonstrated that diabetes increases the risk of Alzheimer's disease by 1.45 times, particularly in women over the age of 65 [74].

Finally, we would like to cite an article that provides an excellent analysis of the factors discussed in this paragraph (as well as those described below). It analyzes data from the Chicago Health and Aging Project and the Rush Memory and Aging Project. Based on this data, a healthy life index was defined, taking into account five elements: a) non-smoking, b) at least 150 minutes of moderate to vigorous physical activity per week, c) light to moderate alcohol consumption, d) adherence to the Dietary Approaches to Stop Hypertension (DASH) diet, e) engagement in cognitive activities in older age. After about 6 years of observation, the results were surprising. Compared to individuals who followed 0 or 1 of the above-mentioned healthy lifestyle elements, the risk of Alzheimer's disease was 37% lower for those who followed 2 or 3 elements and 60% lower for those who followed 4 or 5 elements [75]. This clearly demonstrates how important it is to focus on a multifactorial approach to Alzheimer's disease prevention through lifestyle modification.

Diet

It is not entirely clear how nutrients may affect the prevention of Alzheimer's disease, but it likely occurs through the reduction of neuroinflammatory processes. Inflammation plays an

important role in the pathogenesis of Alzheimer's disease and is associated with increased production of interleukin-1β, interleukin-6 (IL-6), and tumor necrosis factor-α (TNF-α). These cytokines may directly or indirectly participate in amyloidosis, neuronal and cortical atrophy, brain volume reduction, cerebrovascular events such as microbleeds and infarctions, as well as neurodegeneration [43]. Most articles focus on three types of diets: Mediterranean Diet (MD), Dietary Approaches to Stop Hypertension (DASH), and Mediterranean-DASH Intervention for Neurodegenerative Delay diet (MIND).

The Mediterranean Diet has evolved over the years but still primarily relies on the consumption of seasonal fruits and vegetables, fish, olive oil, cheese, eggs, nuts, bread, certain types of meat, and moderate amounts of red wine with meals [44]. The positive impact of the Mediterranean Diet on reducing mortality by lowering the risk of cardiovascular diseases, obesity, insulin disorders, strokes, and neurodegenerative diseases has been demonstrated in numerous studies [45-47]. A study published in 2013 involved 522 individuals at high cardiovascular risk, who were enrolled in a multicenter randomized preventive trial (PREDIMED). Participants were divided into intervention groups—fed a Mediterranean Diet combined with nuts or olive oil—and a control group, which followed a low-fat diet. After 6.5 years, participants were tested using the Mini-Mental State Examination (MMSE) and Clock Drawing Test (CDT). As a result, both intervention groups achieved higher cognitive test scores than the control group, leading to the conclusion that the Mediterranean Diet likely improves cognitive abilities [48]. It was also shown that the Mediterranean Diet can increase cortical thickness in the frontal and parietal lobes, as well as in certain regions of the brain, such as the upper temporal lobe, ventrolateral prefrontal cortex, entorhinal cortex, and fusiform gyrus. These structures mediate memory, executive functions, attention, language processes, and their atrophy is associated with dementia [49].

The Dietary Approaches to Stop Hypertension (DASH) diet was created, as the name suggests, to combat hypertension. It consists of low-fat dairy products, nuts and seeds, fruits and vegetables, lean meats, and carbohydrates [50]. The potassium, calcium, and magnesium found in these products help prevent endothelial dysfunction and relax the smooth muscle of blood vessels [51]. Like the Mediterranean Diet, the DASH diet has anti-inflammatory properties [50], and by preventing the development of hypertension, it also protects against another significant risk factor for dementia [52]. A study published in 2010 demonstrated that participants with

elevated blood pressure who followed the DASH diet showed greater improvement in cognitive abilities compared to the control group [53].

Based on the two diets mentioned above, the Mediterranean-DASH Intervention for Neurodegenerative Delay (MIND) diet was developed. However, it is not a complete combination of the Mediterranean and DASH diets, and there are some differences. The MIND diet emphasizes frequent consumption of leafy green vegetables, does not place as much importance on fruit intake, but recommends consuming large quantities of berries such as blueberries and strawberries (it has been shown that this is associated with a slower decline in cognitive function). Additionally, unlike the Mediterranean Diet, the optimal amount of fish in the MIND diet is one serving per week. Data suggest that the MIND diet has greater benefits in preventing Alzheimer's disease than the Mediterranean and DASH diets, and even moderate adherence to it can have significant preventive properties [54,55].

Not only the above-mentioned diets can reduce the risk of dementia, but individual food components are also associated with this effect. Special attention is given to unsaturated fatty acids omega-3, omega-6, PUFA, and MUFA found in fatty fish, nuts, and vegetable oils, which reduce amyloid-β levels by directing the processing of APP to an alternative pathway [56], stimulate amyloid-β phagocytosis [57], reduce microglial activity [58], improve motor functions, and enhance survival [59]. Additionally, the use of polyphenols, such as curcumin, which have anti-inflammatory, antioxidant, and neuroprotective effects, has shown positive results. Other phytochemicals with similar properties to curcumin include carotenoids, chlorogenic acid, rosmarinic acid obtained from lemon balm, quercetin from white mulberry, resveratrol, and epigallocatechin gallate (EGCG) [60].

Finally, it is worth mentioning the benefits of supplementing with vitamin D, folic acid, vitamin B12, and vitamin A. Studies in animal models have shown that vitamin D supplementation improves memory functions, alleviating amyloidopathy and gliopathy [62]. Folic acid helps reduce homocysteine levels—a major risk factor for dementia. Every increase in homocysteine by 5 μmol/L can raise the risk of Alzheimer's disease by up to 12% [63]. Vitamin B12 exhibits antioxidant properties, modulates cytokines and the inflammatory response, and, along with other B vitamins, supports the survival of nerve cells and

remyelination [64]. In vitro studies have linked vitamin A supplementation to reduced amyloid-β formation and inhibition [61].

Based on numerous articles, it seems that following an appropriate diet has a very promising impact on the prevention of Alzheimer's disease. Unfortunately, the dementia and Alzheimer's disease rates are highest in developing countries (compared to highly developed countries), where the diet, due to financial reasons, mainly consists of carbohydrates and saturated fatty acids, which contribute to the development of hypertension, diabetes, obesity, heart disease, oxidative stress, and neuroinflammatory states. A healthy diet, such as MD, DASH, or MIND, involves much higher costs, and with low incomes, it will unfortunately be ignored, which will not impact the future decline in Alzheimer's disease cases [65].

Physical activity

Physical activity impacts the reduction of dementia risk in multiple ways. Not only does it reduce metabolic and vascular risk factors for dementia by lowering blood pressure or blood glucose levels, but it also decreases stress levels [16]. Moreover, it increases cognitive reserve, which directly helps the brain cope with damage, such as in Alzheimer's disease [13]. A correlation has also been observed between physical activity and increased brain volume [14] as well as hippocampal volume [15]. Additionally, exercise improves brain blood flow, reduces inflammatory responses, and mitochondrial damage, which in turn enhances attention, memory, executive functions, and accelerates thinking processes [17]. Therefore, there are many pathways through which physical activity could influence cognitive function improvement and reduce dementia risk, but how does this translate into reality and clinical studies?

In a two-year study conducted between 2004-2007 on the Perth population in Western Australia, 170 participants over the age of 50, who presented with subjective and mild cognitive impairments but did not meet dementia criteria, were randomly divided into two groups. One group was asked to perform 50-minute, moderate-intensity exercise three times a week, while the control group received educational materials about memory loss, stress management, healthy diet, smoking and alcohol effects, but not about physical activity. Both groups were

assessed every six months using the Alzheimer's Disease Assessment Scale (ADAS-Cog, modified version). The researchers concluded that physical activity had a moderate impact on improving cognitive functions [18]. Twenty years have passed since this study, but the conclusions from other, newer studies are similar [19, 20, 22, 24]. It is important to note, however, that many studies report cognitive function improvement through physical activity but do not directly refer to the reduction of dementia risk or Alzheimer's disease [18-20]. One study addressing this issue is a 2017 meta-analysis, which suggests that physical activity has a stronger protective effect in Alzheimer's disease than in the decline of cognitive abilities in other types of dementia, including vascular dementia [24].

Unfortunately, not all studies come to as optimistic conclusions as the ones above. In 2019, a meta-analysis was published that aimed to analyze 19 prospective cohort studies (lasting more than 10 years) investigating the impact of physical inactivity on the development of dementia. This meta-analysis did not prove that simply combating physical inactivity protects against Alzheimer's disease or other forms of dementia. However, it did observe an increased dementia risk in the subgroup of physically inactive individuals who developed cardiometabolic diseases. The meta-analysis also pointed out that many studies in this field focus on too short observation periods, which could influence the results [21], as studies lasting under 10 years showed a more promising effect of physical activity on dementia prevention than those lasting over 10 years [22]. To confirm the current findings, future studies would need to be conducted on a large scale, over many years, using repeatable and ideally objective measurements, with observations continuing until the death or late old age of all participants [21]. Similar conclusions were drawn by researchers who in 2020 published results from their study on a group of 2394 healthy (in terms of dementia) middle-aged Caucasian men who were observed for an average of 25 years using leisure-time physical activity (LTPA) and occupational physical activity (OPA) questionnaires. They did not find any link between physical activity and the development of dementia or Alzheimer's disease in this group [23].

Researchers are therefore not unanimous about whether physical activity affects the development of dementia and Alzheimer's disease, although many mechanisms have been identified that could explain its impact [13-17]. Regardless of the study outcomes, physical activity should still be promoted as a known, simple, and cost-effective strategy for fighting diabetes, coronary artery disease, and stroke, and indirectly for preventing dementia [23].

CONCLUSIONS

The recognized modifiable risk factors for Alzheimer's disease include: diabetes, hypertension, and obesity in midlife, smoking, depression, lack of cognitive activity or low education levels, and physical inactivity. It turns out that even half of the Alzheimer's disease cases worldwide could potentially be attributed to these factors, and if their prevalence were reduced by 25%, we could decrease the current number of Alzheimer's cases by more than 3 million [42]. Moreover, when appropriate diet, supplementation, and social connections are also taken into account, this number could be further reduced. This offers great hope that a proper lifestyle could protect a large population from developing this currently incurable disease.

DISCLOSURE

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- Receiving funding: Not applicable.

All authors have read and agreed with the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: Not applicable.

Acknowledgements: Not applicable.

Conflicts of Interest: The authors declare no conflict of interest.

Declaration of the use of generative AI and AI-assisted technologies in the writing process. In preparing this work, the authors used ChatGPT for the purpose of improving language and readability. After using this tool, the authors have reviewed and edited the content as needed and accept full responsibility for the substantive content of the publication.

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