

Non-Genetic Risk Factors for Dementia and Alzheimer's Disease

Firas H. Bazzari^{1✉} and Amjad H. Bazzari²

Abstract

Alzheimer's disease (AD) is a multifactorial neurodegenerative disorder linked to multiple genetic and environmental factors. Despite its complex pathology and still undetermined etiology, a number of factors have been found to be closely associated with the incidence of AD. Although the molecular mechanisms linking many of these factors with AD are unclear and not necessarily causative, their identification and control might be key preventative measures. Cardiovascular diseases, diabetes, obesity, and other lifestyle habits are recognized as established risk factors for AD. Other emerging factors investigated as potential contributors to the overall risk of dementia include anemia, obstructive respiratory diseases, vitamin D deficiency, thyroid imbalance, inflammation, and depression. This review summarizes established risk factors; it also provides an insight into emerging factors as modifiable elements, the control of which may reduce the risk of AD and dementia.

Keywords: Environmental factors, cardiovascular diseases, diabetes, obesity, thyroid imbalance, anemia, obstructive lung diseases, vitamin D deficiency

(J Med J 2023; Vol. 57 (3): 206–220)

Received

Accepted

April, 9, 2021

January, 11, 2022

INTRODUCTION

Dementia is one of the most prevalent diseases among the elderly and is associated with increased morbidity and mortality rates [1]. The number of dementia patients is expected to reach 81.1 million by 2040, with a significant socioeconomic burden [2, 3]. Although various types of dementia have been identified, Alzheimer's disease (AD) is the leading cause of dementia, representing 60–80% of all cases [4]. Many agents and preparations have been investigated for therapeutic efficacy in AD; however, available drug treatments only provide symptomatic improvement, and disease-modifying therapies are still lacking [5, 6].

AD is characterized by a number of

histopathological hallmarks, including: amyloid-beta ($A\beta$) plaques, neurofibrillary tangles (NFTs), and neuronal degeneration [7]. After the isolation of $A\beta$ proteins homologous to AD-associated fibrils from patients with Down syndrome, and the identification of amyloid precursor protein (APP) genetic mutation in familial AD (FAD), the amyloid cascade hypothesis (ACH) was introduced. This states that $A\beta$ is the leading cause of AD pathology [8–10]. Moreover, the detection of presenilin mutations linking $A\beta$ overproduction with FAD has also prompted the ACH to become the most widely adopted hypothesis for AD [11]. The ACH has directed researchers to investigate $A\beta$ -induced pathological effects, and this has greatly improved our understanding of AD-associated neuroinflammation, oxidative and metabolic stress, NFT formation, and excitotoxicity that

¹ Pharmacy Department, Faculty of Allied Medical Sciences, Arab American University, Jenin, Palestine.

² Faculty of Pharmacy, Al-Quds University, Abu Dis, Jerusalem, Palestine.

✉Corresponding author: firas.bazzari@aaup.edu

ultimately lead to neurodegeneration [12–15].

However, the majority of previous observations were derived from early-onset FAD cases, in which a direct cause of A β overproduction was identifiable; however, FAD represents only a tiny percentage of all AD cases, while the remainder is sporadic AD (SAD) that constitutes the majority of late-onset cases occurring primarily after 65 years of age [16]. Although multiple other hypotheses regarding AD pathogenesis have been proposed, a specific cause or ‘trigger’ of SAD remains unidentified [17–19]. Despite the apolipoprotein-E ϵ 4 (ApoE4) allele polymorphism being linked to an increased risk of SAD, it is not detected in all patients and may contribute to a proportion of the overall risk [20, 21]. It has been suggested that SAD patients inherit 60–80% of AD risk, with the remainder being purely environmental; moreover, the genetic risk is proposed to be additive of a large number of genes, each representing a small fraction of the overall risk [16, 22].

According to the World Alzheimer Report, AD prevalence varies significantly across different regions and socioeconomic groups. This can be due to several factors, such as chemical/microbial exposure, diet, lifestyle habits, and the incidence of other diseases [23]. The wide range of environmental risk factors associated with late-onset AD, which are found to significantly affect not only AD risk but also its progression, implies further complexities but could still provide key insights into the underlying etiology and pathophysiology of AD.

Established modifiable risk factors

Cardiovascular diseases

It is evident that there is a strong link between cardiovascular (CV) conditions occurring in midlife and dementia. In addition to stroke [24], multiple other CV diseases are associated with increased AD risk through various mechanisms mostly related to acute and/or chronic cerebral ischemia.

Hypertension (HTN) is one of the most prevalent CV diseases and midlife HTN is found to increase AD risk significantly, which correlates with elevated systolic pressure [25].

HTN has been linked to increased risk of stroke, silent cerebral ischemia, atherosclerosis and development of white matter lesions [26]. Moreover, the use of commonly prescribed antihypertensive medical agents is found to significantly reduce AD incidence [27].

Heart failure (HF) is another CV disorder linked to cognitive impairment. In a population-based cohort study in Sweden, HF was associated with a higher risk of developing AD and dementia [28]. Global reductions in cerebral blood flow in HF patients precipitate regional and functional deficits similar to the reported deficits in early-stage AD [29]. Additionally, the cardiac index value is found to correlate inversely and significantly with dementia and AD incidence [30]. Due to the lack of a direct AD pathogenesis mechanism arising from HF hypoxia and neurohormonal alterations, multiple protective measures, in addition to pharmacological treatment, have been proposed in relation to HF and AD, including antioxidant supply, prevention of peroxynitrite/oxygen radical formation and nitric oxide donor supplementation in an individualized manner [31].

Coronary artery disease (CAD) has also been investigated as an AD risk factor. Besides thromboembolic events, CAD is found to be associated with non-amnesic mild cognitive impairment and cerebral hemodynamic alterations that correlate with reduced cognitive function and obesity [32, 33]. Using coronary artery calcium (CAC) as a marker of coronary artery atherosclerosis in the elderly, an elevated CAC value has been found to be a major determinant of mortality and is associated with a higher age-specific incidence of dementia in comparison to CAD [34].

Other CV diseases that increase dementia risk include atrial fibrillation (AFib), which is independently associated with an increased risk of all types of dementia, especially vascular dementia and AD [35]. Additionally, hypercholesterolemia is considered an early AD risk factor which accelerates A β pathology and enhances its accumulation, whereas lowering blood cholesterol level using statins can reduce AD prevalence [36–39].

Diabetes

Cognitive decline is considered a long-term effect of diabetes mellitus (DM). In a longitudinal cohort study, DM patients had a higher risk of developing AD compared to non-diabetics [40]. In another dementia-free cohort study with six years' follow-up on DM patients aged 75 years and older, DM was associated with an elevated incidence of AD and vascular dementia [41]. While DM significantly increases the risk of AD incidence, the use of oral hypoglycemic agents may not illustrate any benefit in ameliorating AD risk [42]. Multiple molecular mechanisms linking DM to AD pathogenesis have been identified, including: oxidative stress, protein processing defects, abnormal insulin signaling, neuro-inflammation and mitochondrial dysfunction [43–45]. Accordingly, hyperinsulinemia associated with insulin resistance accelerates AD pathology, while improved insulin signaling is found to attenuate cognitive defects and AD pathology in rodent models [46, 47].

Obesity

A strong link between elevated body mass index (BMI) value, a marker of obesity, and multiple CV diseases, as well as cognitive decline, is well established. In a multiethnic-population cohort study, overweight (i.e., BMI 25–29.9) and obese (i.e., BMI>30) participants had a 35% and 74% increased risk of developing dementia, respectively, compared to a normal weight group [48]. In a larger and more diverse cohort, midlife obesity was found to be a strong predictor of both AD and vascular dementia, independent from other comorbidities (i.e., stroke, DM and CV diseases) [49]. In a 2009 meta-analysis assessing AD risk in association with obesity and DM, both disorders significantly and independently increased AD risk, in which the pooled effect size of obesity was even higher than DM for AD [50]. Endothelial dysfunction resulting in cerebral hypoperfusion, through inhibited nitric oxide production, is proposed to account for the increased AD incidence in obesity [51]. In addition, various interactions between obesity, inflammation, sex hormones and ApoE4, as well as the roles of

adipocytokines (e.g., leptin and adiponectin) are all suggested to contribute to the overall risk of AD [52, 53].

Lifestyle factors

Variations in lifestyle, including dietary habits, physical activity and smoking, were investigated in relation to dementia and AD risk. Different dietary patterns were observed to alter the risk of multiple disorders significantly, including AD [54]. Mediterranean diet was found to reduce AD risk, while western diet consumption has been found to alter hippocampal functions and elevate the risk of both AD and obesity [55, 56]. Adequate intake of fruits, vegetables, fish and omega-3 fatty acid supplements can also reduce AD risk [57]. In a prospective cohort, physical activity was independently associated with a lower hazard ratio for AD [58]. In a randomized controlled trial, increased physical activity was observed to improve cognition in non-demented participants who reported memory defects [59]. An analysis controlling for any affiliation by tobacco industry companies and an analytic cohort evaluating the association between midlife smoking and the risk of AD, have found that smoking significantly increases the risk of dementia and AD, as smoking is associated with the development of several CV diseases and direct endothelial injury [60, 61].

Emerging risk factors**Anemia and hemoglobin level**

Over the past two decades, the effects of iron deficiency anemia (IDA) and iron supplementation have been investigated in relation to cognitive functions with multiple proposed hypotheses [62]. Many subsequent studies on iron deficiency, for instance in non-anemic adolescents [63] and infants with IDA [64], have revealed the important roles of iron not only in cognition but also in overall brain functioning and development, as well as in relation to dopaminergic transmission, myelination, gene expression, and neurometabolism [65, 66]. Moreover, anemia is reportedly associated with cognitive decline in the elderly and is suggested to be a risk factor for AD [67]. Although most previous studies focused on iron and IDA, a recent cross-

sectional study found that multiple anemia subtypes, including normocytic, microcytic and macrocytic, were similarly associated with reduced cognitive functions; in addition, the study reported that elevated hemoglobin (Hb) is non-significantly associated with reduced cognition [68].

Furthermore, the severity of anemia in the elderly, determined via Hb level, directly correlates with the incidence of dementia, as a 2017 screening study based in Korea demonstrated that the risk for dementia is directly correlated with the severity of anemia, and that anemia is an independent risk factor for dementia [69]. In a study involving 2,552 elderly individuals (mean age of 76.1 years), anemic participants had a significant increase in the incidence of dementia compared to non-anemic patients, despite adjustment for demographic factors (i.e., renal function, ApoE4 status, presence of comorbidities, and baseline cognitive scores) [70]. In a prospective cohort analysis, both reduced and elevated Hb levels correlated with increased AD risk and accelerated decline in cognitive functions [71]. Both the α and β chains of Hb have been found to be normally expressed by neurons. Hence, this suggests a possible role for Hb in dementia and AD besides determining the total oxygen carrying capacity and meeting physiological brain requirements [72]. In addition, a general decline in neuronal Hb expression has been observed in AD and other neurodegenerative disorders, such as Parkinson's disease, in a neuron subtype-specific manner [73].

Multiple studies have focused on the possible roles of neuronal Hb in AD; for instance, when A β was injected in transgenic APP/PS1-mutant mice, it interacted with Hb iron-containing heme, as Hb droplets were enveloped by A β -formed structures [74]. Moreover, Hb is observed to localize with A β plaques and promote A β deposition and oligomerization, suggesting that elevated levels of brain Hb might be involved in AD pathogenesis [75]. However, in a study evaluating blood profile alterations, AD patients had reduced levels of red blood cell count, Hb and hematocrit; on the other hand, the

mean cell volume, mean cell hemoglobin, red cell distribution, and width-SD values were elevated [76]. Furthermore, AD itself is found to increase the risk of anemia, as AD patients have lower total Hb, mean cell Hb and packed cell volume; this reveals further AD-related complications and complex interactions with anemia and Hb [77].

Obstructive lung diseases

Multiple respiratory diseases are reported to increase the incidence of dementia, such as adult asthma, chronic obstructive pulmonary disease (COPD) and obstructive sleep apnea (OSA). Inflammatory disorders are also believed to contribute to AD progression and, in a longitudinal study evaluating the link between atopy and AD, atopy was found to increase dementia risk, and a history of asthma in AD patients was associated with increased mortality [78]. In addition, improving asthma control over a one-year treatment course resulted in a significant improvement in minimal state examination (MMSE) scores in participants with dementia, mild cognitive impairment and normal cognition [79]. A 2013 Cooper Centre study revealed a strong interconnection between impaired cognition and asthma in the elderly, which accounted for a 78% increased risk compared to control [80]. Similarly, another cohort has demonstrated a significant elevation in dementia risk in patients with asthma, which is markedly increased in patients with frequent asthma-related hospitalization and exacerbations [81]. Moreover, asthma occurring in both mid- and late life is found to increase the risk for all types of dementia and AD [82]. Therefore, maintaining asthma control and careful monitoring, especially with adult-onset asthma, are important for reducing dementia risk.

COPD is a disease of the elderly with high mortality rates and systemic complications arising from chronic hypoxia and hypercapnia. COPD patients are observed to suffer from cognitive impairment and elderly patients with poor COPD control and medication adherence display abnormal delayed-recall and significant reduction in verbal memory [83]. It is also suggested that COPD leads to the development

of subclinical encephalopathy, independent from other comorbidities, which at advanced stages may lead to cognitive impairment, memory deficits, and confusion which are directly related to COPD severity [84]. It is reported that COPD-related cognitive dysfunction is unlikely to be caused entirely by associated hypoxemia, hypercapnia, comorbid diseases, fatigue, smoking and general health state; however, the incidence of cognitive impairment has been found to be higher in hypoxemia and is suggested as being responsible for increased disability and mortality [85]. In a 2015 retrospective cohort, COPD was associated with a high risk for dementia, which significantly increased with more frequent COPD-associated exacerbations [86]. A nationwide cohort on Taiwanese individuals illustrated a significant elevation in multi-adjusted COPD hazard ratios for developing AD or Parkinson's disease [87]. Furthermore, a study involving 2,000 participants with 25 years' follow-up showed that both midlife asthma and COPD are associated with a higher risk (two-fold) of developing mild cognitive impairment and dementia [88]. COPD and AD share common risk factors, such as smoking and age, and in addition COPD is found to aggravate a number of AD underlying pathologies, such as systemic inflammation, oxidative stress, hypoxia and vasculopathies [89].

OSA is a common disorder that was recently investigated as a potential contributor to increased AD incidence [90]. The characteristic feature of OSA is the repetitive pharyngeal airway collapse, which occurs during sleep due to various anatomical and physiological factors [91]. In a meta-analysis evaluating the relationship between OSA and AD, OSA aggregate odds ratio in AD was 5.05 (i.e., AD patients are five times more likely to present with OSA compared to age-matched controls) and OSA patients were observed to have altered cerebral blood flow as well as increased oxidative stress [92]. OSA is also attached to a number of AD-associated vascular pathologies, for instance, alterations in the intima-media thickness of the common carotid arteries and

hypercapnia-induced cerebral reactivity; in addition, AD-associated cognitive impairment is found to be directly related to the severity of OSA [93]. Biochemical analysis has shown that OSA patients have increased cerebrospinal fluid (CSF) levels of lactate, lower CSF A β 42 concentration and elevated tau/A β 42 ratio that correlated with memory deficits and lower cognitive performance compared to control and continuous positive airway pressure-treated groups [94].

Vitamin D deficiency

Besides its key functions in bone mineralization and calcium homeostasis, vitamin D (Vit-D) is reported to exhibit immunoregulatory, neuroprotective and anti-tumor effects in the nervous system [95]. Vit-D deficiency (VDD) is considered a global health concern that affects individuals from all age groups [96]. VDD is associated with increased incidence and mortality risk for multiple metabolic and CV diseases, including HTN, HF, obesity and diabetes [97]. Recently, the association between VDD and AD was extensively investigated. In a study of 1,658 non-demented elderly, VDD significantly increased the risk for all-cause dementia and AD, as participants with severe (i.e., 25 (OH) D<25 nmol/L) and moderate (i.e., 25–50 nmol/L) VDD had increased multi-adjusted hazard ratios for AD, compared to control [98]. In a population-based cohort in Italy, VDD was found to increase AD risk independently and promote AD progression; in addition, low Vit-D levels (i.e. <75 nmol/L) may also serve as a predictive tool for developing cognitive impairment [99]. Based on the ubiquitous alterations of Vit-D-related genes, transporters, receptors and metabolic enzymes in AD, together with the overlap of VDD-induced damage and loss of neuroprotection, it is suggested that VDD can be a fundamental contributor to AD risk and pathology [100]. In order to avoid further complications, screening for VDD in the elderly and adequate supplementation were recommended; nonetheless, due to lack of specificity, VDD should not be used for AD and dementia prognosis [101]. In several studies, VDD

accelerated the decline in cognitive function, increased AD risk, accelerated visual but not verbal memory decline, reduced total hippocampal volume, and correlated with inferior neuropsychological brain functions [102–106]. Multiple mechanisms mediating Vit-D neuroprotection have been proposed, such as promoting neuronal survival and maintenance through the induction of nerve growth factor and glial-derived neurotrophic factor synthesis, regulation of neuronal intracellular calcium dynamics, suppression of AD-related neuro-inflammation, counteraction of oxidative stress, and regulation of A β /APP metabolic pathways [107]. A recent study evaluating the effects of genetically reduced Vit-D in relation to AD and cognitive dysfunction, in which certain single-nucleotide polymorphisms linked to Vit-D (25OHD) metabolism were used, found that genetic reduction of Vit-D results in a significant increase in AD odds ratio; hence, it can be concluded that VDD could be a causative factor for AD [108].

Thyroid imbalance

The thyroid hormone (TH) is one of the major hormones necessary for normal cognitive function and brain maturation at different developmental stages [109]. Multiple transport mechanisms of TH into the young and adult brains have been identified and shown to be differentially expressed in various brain regions [110]. Studies investigating TH functions in rodent brains via TH receptor deletion, induced hypothyroidism, or TH supplementation have highlighted the importance of TH in serotonergic transmission, motor functioning, behavior, and mood [111, 112]. In rats, TH played a critical role in regulating hippocampal morphology, survival, differentiation, and neurogenesis, which may account for the hypothyroidism-related cognitive dysfunction in adults [113]. Recent research on the interconnection between thyroid function and dementia shows that both reduced and elevated TH levels might be risk factors for AD. The Rotterdam prospective study introduced early evidence of the involvement of TH in the development of dementia, as the study results

illustrated an association between subclinical hyperthyroidism and an increased risk of AD (three-fold) that correlated with reduced thyroid stimulating hormone (TSH), elevated T4, and lowered thyroid peroxidase serum antibody levels [114]. This was followed by another study in which the participants had reduced TSH levels, even at the lower end of the normal range, and a higher risk of AD after adjustment for confounding variables and CV risk factors [115]. Elevated serum TSH levels are also found to correlate with AD, as both high and low TSH serum levels in euthyroid participants were found to increase AD risk in women but not men [116]. Moreover, AD patients with subclinical hypothyroidism are observed to have reduced regional cerebral blood flow in the thalamus and the temporal lobe [117]. However, higher TSH levels were reported to reduce AD risk and associate with better cognitive performance, while elevated free T4 increased dementia risk in a non-vascular pathway [118]. In addition, elevated T4 levels were associated with higher NFT and neuritic plaque numbers in the cerebral cortex of an AD autopsied sample [119]. Two studies titled ‘The Health, Aging and Body Composition’ and ‘Sao Paulo Aging and Health’ reported that subclinical hyperthyroidism, but not subclinical hypothyroidism, is related to higher AD and dementia risk [120, 121]. Multiple pathways were proposed to explain the possible mechanisms linking direct TH functions, vascular effects, and TSH roles in neurodegeneration [122]. However, the interactions between TH and cognitive function are complex and not fully understood, which necessitates further investigations.

Miscellaneous risk factors

Traumatic brain injury (TBI) is one of the earliest proposed risk factors for dementia. A recent retrospective cohort of 188,000 elderly individuals above 55 years of age found that a history of TBI was associated with increased AD risk [123]. TBI is believed to predict AD development even when occurring early in life; however, a recent study on AD patients with a history of TBI has demonstrated age-dependent outcomes, in which AD patients who had a TBI

prior to age 22 years have achieved higher cognitive scores compared to older-onset individuals [124].

Inflammation is a major component of AD pathology, and multiple systemic inflammatory and autoimmune diseases were investigated as potential contributors to AD risk. Rheumatoid arthritis, osteoarthritis, Sjogren's syndrome, and systemic lupus erythematosus are all found to increase the risk of dementia and AD [125–128]. Both acute and chronic inflammatory episodes that elevate tumor necrosis factor- α (TNF- α) are found to accelerate AD-related cognitive decline [129]. On the other hand, gout patients are found to exhibit lower AD risk in support of the various proposed roles of uric acid and its derivatives in neuroprotection against stroke and neurodegenerative disease [130–132].

The interactions between neuropsychiatric diseases and AD are complex; for instance, AD patients are at a higher risk of developing delirium, apathy, agitation, depression and psychosis [133, 134]. On the other hand, certain psychiatric disorders are also suggested to play a role in elevating AD risk. Delirium represents an acute transient state of confusion that alters perceptions and cognitive functions, which is associated with increased AD incidence and cognitive decline in the elderly [135, 136]. Similarly, schizophrenia is also associated with increased dementia risk [137]. In the case of depression, it is observed that late-life depression carries a two-fold increase in dementia risk as well [138]. Furthermore, a recent longitudinal study on women observed that both early and late life depression correlated with a higher AD incidence [139]. The use of antidepressants is found to reduce the risk of AD development, while selective serotonin reuptake inhibitors (SSRIs) use in the elderly was reported to increase the risk of AD compared to severely depressed non-users [140, 141].

It is well known that B vitamins, especially B12, are essential for neuronal health and indeed Vit-B12 deficiency is a common issue among the elderly and AD patients [142]. In animal models, B12 deficiency induces oxidative stress, impairs

memory retention and elevates hippocampal A β level and deposition when combined with folate and B6-deficient diet in AD mice [143, 144]. In human subjects, B vitamin treatment containing folic acid, B12, and B6 reduces AD-associated brain atrophy [145].

Besides OSA, sleep quality and duration are found to correlate with dementia incidence and overall risk. In a 2015 study, dementia-free elderly who experienced sleep disturbances had a 27% increase in the risk of developing dementia [146]. In a prospective study on elderly women, both short and long sleep durations (i.e., ≤ 6 and ≥ 8 h/night) increased dementia risk to a similar degree, in a V-shaped correlation [147].

Lastly, multiple medical agents are suggested to elevate the risk of and/or exacerbate dementia and AD complications, such as drugs with anti-cholinergic activity (e.g., digoxin, metoprolol, warfarin) [148]. Therefore, extra care should be taken when prescribing to the elderly with regard to over- or under-prescribing, drug interactions, vulnerability to side effects, medication adherence, and proper monitoring.

CONCLUSIONS

Despite incomplete understanding of the mechanisms linking many of the above-mentioned factors with elevated AD risk, current evidence highlights the vital role of non-genetic factors in the development of AD and dementia. Moreover, adequate control of various health conditions, particularly CV diseases, is generally found to be effective in reducing AD risk. Similarly, even to a lesser extent, promising outcomes can be expected with early identification and proper management of the emerging risk factors. However, more studies are needed to investigate possible causal relationships that would provide valuable insights into SAD etiology. Compared to the challenging treatment and development of AD medications, undertaking preventative measures is a more feasible and straightforward approach. Non-genetic risk factors for dementia can be identified through regular screening tests; in

addition, many of these factors are lifestyle-associated, such as dietary habits and physical

activity; thus, increased awareness and patient education are vital.

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عوامل الخطر الغير وراثية لمرض الخرف والزهايمر

فiras حسن بزازي¹، أمجد حسن بزازي²

¹ قسم الصيدلة، كلية العلوم الطبية المساندة، الجامعة العربية الأمريكية، جنين، فلسطين.

² كلية الصيدلة، جامعة القدس، أبو ديس، القدس، فلسطين.

الملخص

الخلفية والأهداف: الزهايمر هو أحد الأمراض العصبية الخطيرة والمُنهكة للمرضى ويعد من أهم مسببات الخرف لدى كبار السن. على الرغم من وجود عدد من الفرضيات المقترحة إلا أنه لا توجد صورة واضحة لتفسير وفهم آلية حدوث المرض الى يومنا هذا. في عدد كبير من الدراسات السابقة تم التعرف على العديد من عوامل الخطر المرتبطة بزيادة نسبة الإصابة بالزهايمر، ويعد التعرف على عوامل الخطر هذه والحد منها من أهم الإجراءات الوقائية المتاحة لتقليل خطر الإصابة بالزهايمر خاصة في غياب علاجات فعّالة للمرض. ولأن النوع الفردي من المرض (الذي ينتج بسبب عوامل غير وراثية / بيئية) يشكل النسبة الأكبر من مجمل الحالات.

منهجية الدراسة: سنقوم هذه الدراسة بالتركيز على عوامل الخطر الغير وراثية للمرض. وتتضمن قائمة عوامل الخطر الغير وراثية لمرض الزهايمر العديد من الأمراض والاعتلالات المختلفة، منها ما تم تأكيده واعتماده بشكل قاطع كعوامل خطر للمرض وتشمل: أمراض ارتفاع ضغط الدم، فشل القلب، تصلب الشرايين التاجية، ارتفاع كوليسترول الدم، السكري، السمنة وبعض العادات اليومية المُضرّة بالصحة مثل التدخين. وفي الكثير من الدراسات الحديثة تم تقديم دليل علمي جديد يكشف عن العديد من عوامل الخطر الأخرى وتشمل: فقر الدم، الربو، أمراض انقطاع التنفس والانسداد الرئوي المزمن، نقص فيتامين د، اعتلالات الغدة الدرقية، الأمراض المسببة للالتهابات المزمنة وبعض الأمراض العصبية والنفسية. تهدف هذه الدراسة الى عمل مراجعة شاملة لما هو متاح من بيانات ونتائج العديد من الدراسات الحديثة التي تعطي دليل علمي يوثق ارتباط بعض الأمراض والاعتلالات كعوامل خطر تزيد من نسبة حدوث الزهايمر، بحيث توفر هذه الدراسة مرجع عام وشامل لآخر ما تم التوصل اليه حديثاً في هذا المجال.

الكلمات الدالة: العوامل البيئية، أمراض القلب والأوعية الدموية، السكري، السمنة، اعتلالات الغدة الدرقية، نقص فيتامين د، فقر الدم، الانسداد الرئوي المزمن.