Mohamed Khider University of Biskra Université Mohamed Khider de Biskra

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BOUFRIOUA Abderrahman

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Retrospective descriptive and analytical study of the major factors associated with Alzheimer's disease

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Jury :

Dr.	ABBA Abderrahman	Grade	University of Biskra	Chair
Dr.	YAACOUB Fadjria	MAB	University of Biskra	Rapporteur
Dr.	MEDJADBA Aicha	Grade	University of Biskra	Examiner

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All thanks, appreciation and respect to my family, relatives and friends.

Dedication

To the pure soul of my father. The best father in the world, and all the words in the world cannot describe this rare man. May God have mercy on him and grant him Paradise. This work is a tribute to his memory, love, and support.

To the most beautiful mother in the world, she is a woman with a beautiful face and graceful features, beautiful in her presence, her words, her advice, her nurturing, her kindness, and her sense of humor. Truly, she is beautiful in every way.

To my beloved sister, unmatched in heart, spirit, and bond and her beautiful family

To my brothers, who are truly one of a kind, no one could ask for better.

To my relatives and friends whom I love and who love me.

I dedicate this humble work to you…

Contents

List of figures

List of abbreviations

AD: Alzheimer's disease

EOAD: Early-onset Alzheimer's disease

APP: Amyloid Precursor Protein

PSEN1: Presenilin 1

PSEN2: Presenilin 2

APOE: Apolipoprotein E

T2D: Type 2 Diabetes

Aβ: Amyloid Beta

Aβ42: Amyloid Beta 42

Aβ40: Amyloid Beta 40

NFTs: Neurofibrillary tangles

sAPPα: Soluble amyloid precursor protein alpha

MMSE: Mini-Mental State Examination

MINI-Cog: Mini Cognitive Test

AD8: Ascertain Dementia 8-item Questionnaire

PDD: Parkinson's Disease Dementia

CT: Computed Tomography

MRI: Magnetic Resonance Imaging

PET: Positron Emission Tomography

TSH: Thyroid Stimulating Hormone

CSF: Cerebrospinal Fluid

P-TAU: Phosphorylated Tau Protein

FPG: Fasting Plasma Glucose

mm HG: Millimeters of Mercury

ECG: Electrocardiogram

ACE: Angiotensin-Converting Enzyme

ARBs: Angiotensin II Receptor Blockers

IADL: Instrumental Activities of Daily Living

MoCA: Montreal Cognitive Assessment

MMPI: Minnesota Multiphasic Personality Inventory

sMRI : Structural Magnetic Resonance Imaging MCI

^{11}C-PIB: Carbon-11 Pittsburgh Compound B18F

^{18}F: Fluorine-18

AV1451: Flortaucipir

TREM-2: Triggering Receptor Expressed on Myeloid Cells 2

TSPO: Translocator Protein

YKL-40: Chitinase-3-like Protein 1 (CHI3L1)

NFL protein: Neurofilament Light Chain

GFAP: Glial Fibrillary Acidic Protein

BBB: Blood-Brain Barrier

DNA: Deoxyribonucleic Acid

ROS: Reactive Oxygen Species

NAD+: Nicotinamide Adenine Dinucleotide (Oxidized Form)

ATP: Adenosine Triphosphate

IGF-1: Insulin-like Growth Factor 1

mTOR : Mechanistic Target of Rapamycin

AMPK: AMP-Activated Protein Kinase

LMICs: Low- and Middle-Income Countries

HR: Hazard Ratio

NF-κB: Nuclear Factor Kappa-Light-Chain-Enhancer of Activated B Cells

RR: Relative Risk

OR: Odds Ratio

APOE ε4: Apolipoprotein E epsilon 4

CR1: Complement Receptor 1

BIN1: Bridging Integrator 1

PICALM: Phosphatidylinositol Binding Clathrin Assembly Lymphoid-Myeloid leukemia **protein**

MAPT: Microtubule-Associated Protein Tau

RNA: Ribonucleic acid

ATXN1: Ataxin-1

ADAM10: A Disintegrin and Metalloproteinase Domain-containing protein 10

CLU: Clusterin (Apolipoprotein J)

CD33: sialic acid-binding immunoglobulin-like lectin

EPHA1: Ephrin type-A receptor 1

DSM-IV: Standardized criteria for the classification and diagnosis of mental disorders.

CI: Confidence Interval

FH: Family History

BP: Blood Pressure

SBP: Systolic Blood Pressure

CYP4A: Cytochrome P450 enzymes

TRPC6: Transient Receptor Potential Canonical 6

20-HETE: 20-Hydroxyeicosatetraenoic acid

MMPs: Matrix Metalloproteinases

NADPH: Nicotinamide Adenine Dinucleotide Phosphate, reduced form

DM: Diabetes Mellitus

GSK-3: Glycogen Synthase Kinase-3

PI3K: Phosphoinositide 3-Kinase

AGEs: Advanced Glycation End Products

DYRK1A: Dual-specificity Tyrosine-(Y)-phosphorylation Regulated Kinase 1A

IRS: Insulin Receptor Substrate

AChEIs: Acetylcholinesterase Inhibitors

Ach: Acetylcholine

RCT: Rondomized Controlles Tri

Introduction

Introduction

Alzheimer’s disease (AD), the leading cause of dementia, is responsible for around 60–80% of all cases. It is a progressive neurodegenerative condition that predominantly impacts older individuals and is marked by a steady decline in cognitive abilities (Rostagno, 2022).

In 2015, it was estimated that approximately 46.8 million individuals worldwide were living with dementia. This figure represents a nearly 30% increase-equivalent to 9.9 million new cases-compared to the incidence reported by the World Health Organization (WHO) in 2010. The highest rates of incidence were recorded in Asia (49%), followed by Europe (25%) and the Americas (18%) (Dos Santos Picanco et *al*., 2018).

The accumulation of amyloid-β (Aβ) in both the brain tissue and cerebral blood vessels, along with the formation of intraneuronal neurofibrillary tangles and the progressive degeneration of synapses, represents the core neuropathological characteristics of Alzheimer’s disease (AD). However, the exact mechanisms that initiate and propel the disease's progression are still not fully understood (Long & Holtzman, 2019).

Alzheimer's disease is a disease of unknown cause and is a complex mixture of contributing factors. This indicates that understanding the nature of these factors and studying them more deeply, as well as their connection to Alzheimer's disease, contributes to developing strategies to prevent this disease and target treatments (Edwards Iii et *al*., 2019).

Given that the exact cause of Alzheimer's disease is still unidentified, researchers have turned their attention to examining the range of factors that are linked to or occur alongside the condition. This has prompted a detailed investigation into the most frequently associated risk factors and an inquiry into the reasons behind their particular significance.

The study seeks to determine why some risk factors appear to be more common than others by describing cases diagnosed with Alzheimer's disease and identifying the most significant associated disorders and conditions. This is followed by conducting a synthesis of research from multiple studies and analyzing them to demonstrate, from both statistical and biological perspectives, that the identified factors are indeed risk factors contributing to the emergence of Alzheimer's disease.

Section I

Bibliographic Section

Chapter 1

Alzheimer's Disease

1. Definition of Alzheimer's disease

Alzheimer’s disease is the leading cause of dementia (70–80% of all dementia cases), it is a progressive neurodegenerative disease, a broad term describing memory loss and other cognitive impairments severe enough to disrupt daily functioning. Most individuals diagnosed with Alzheimer’s disease are aged 65 or older. When the condition develops in someone younger than 65, it is classified as early-onset Alzheimer’s (DeTure & Dickson, 2019).

2. Etiology and risk factors

Alzheimer’s disease is a disease of unknown cause. However, it is widely considered to have a multifactorial etiology, with various risk factors contributing significantly to its development (Povova et *al*., 2012).

2.1. Non-modifiable risk factors

2.1.1. Age

Age stands out as the most significant. The prevalence of Alzheimer’s dementia rises markedly with advancing age: approximately 5% of individuals aged 65 to 74, 13.2% of those aged 75 to 84, and 33.4% of individuals aged 85 and older are affected by the condition (Hebert et *al*., 2013).

2.1.2. Genetics

The vast majority of AD cases are sporadic, where there is no dominant genetic cause (G. M et *al*., 2015).

The primary genetic risk factors associated with early-onset Alzheimer's disease (EOAD) are three key genes (Mutations in these genes): amyloid precursor protein (APP), presenilin 1 (PSEN1), and presenilin 2 (PSEN2) (Modarresi et *al*., 2011).

Recent research have identified the ε4 allele of the APOE gene as the most significant genetic risk factor associated with the development of AD, especially sporadic AD (Z. L et *al*., 2015).

2.1.3. Family history

The likelihood of developing Alzheimer's dementia is higher for people who have or had a parent or sibling (a first-degree family) with AD than for those who do not. Approximately

25% of individuals aged 55 and older have a family history of dementia. For individuals with such a family history, the lifetime risk of developing dementia is around 20%, compared to 10% in the general population (Loy et *al*., 2014).

2.2. Modifiable risk factors

Age, genetics and family history contribute to the development of AD and are non-modifiable risk factors. Furthermore, AD can also be caused by modifiable risk factors related to manageable medical issues and lifestyle decisions. These risk factors may contribute to the etiology and pathogenesis of AD through their own biological pathways: vascular diseases, diabetes mellitus, traumatic brain injury, epilepsy, depression, and lifestyle which includes physical activity, sleep disturbance, diet, smoking, alcohol (Edwards Iii et *al*., 2019).

2.2.1. Cardiovascular health factors

Changes in vascular system lead to a decrease in cerebral perfusion, causing brain malfunction and cognitive decline (C, 2013). thereby presenting the idea of the vascular hypothesis of AD. According to this hypothesis, vascular disorders enhance the neuropathologic hallmarks of AD (de la Torre, 2018). A history of prehypertension and hypertension during midlife or later in life raises the likelihood of developing dementia and worsens the neuropathology associated with AD (Gottesman et *al*., 2017).

2.2.2. Type 2 diabetes

There is such a strong epidemiological connection between AD and T2D that some researchers classify AD as type 3 diabetes. T2D is suggested to raise the risk of AD and dementia from 1.3 to 5.5 times. According to Rotterdam study conducted in the 1990s, T2D doubles the risk of AD and dementia (Li et al., 2015). Patients with type 2 diabetes have a 60 % higher chance of developing dementia than people without diabetes (Chatterjee et *al*., 2016).

3. Pathophysiology/Pathogenesis

Alzheimer's disease (AD) is characterized by certain pathological alterations that take place inside the brain. These alterations start in middle age and develop gradually (Cazarim et *al*., 2016).

- Pathological changes at the macroscopic level: which involves shrinkage or atrophy of the hippocampus and cerebral cortex (A. L et *al*., 2012).

- ❖ Pathological changes at the microscopic level: the two central pathological hallmarkers of AD are: extra neuronal β-amyloid deposits (senile plaques), and intraneuronal neurofibrillary tangles (NFTs) by accumulation of hyperphosphorylated tau protein (Tiwari et *al*., 2019).

3.1. β-amyloid hypothesis

The pathophysiological explanation for AD that is presently most commonly accepted is the β-amyloid Hypothesis (Paroni et *al*., 2019).

Aβ peptide is formed after altered cleavage of a larger Amyloid precursor protein (APP). APP is a transmembrane protein consisting of about 770 amino acids and produced by a variety of cells, including neurons. APP is typically cleaved by enzymes known as secretases (α, β and ɣ secretases) to generate different peptide fragments necessary for neuronal activities (Suzuki et *al*., 2023).

Under physiological conditions, APP is cleaved by α-secretase rather than β-secretase through a non-amyloidogenic pathway to produce the soluble sAPPα fragment. In pathological situations (Fig. 1), Aβ is generated from APP by β-secretase followed by γ secretase through an amyloidogenic pathway (Soldano & Hassan, 2014).

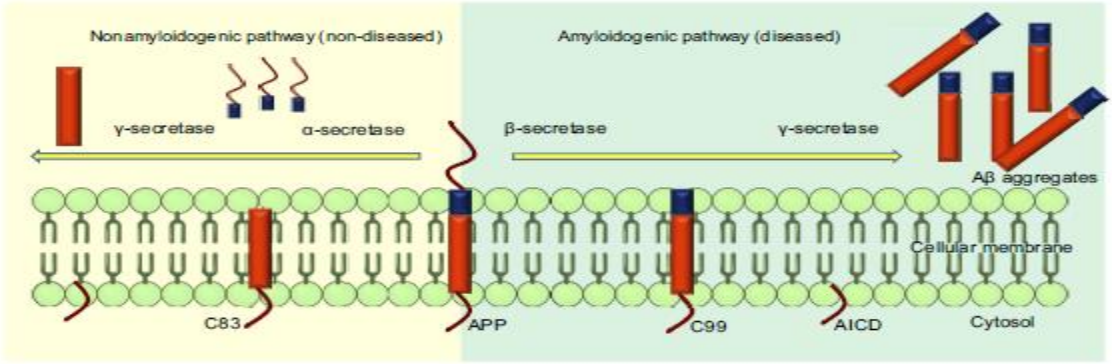

Figure 1. Alternative splicing of APP in amyloidogenic and nonamyloidogenic pathways (Tiwari et *al*., 2019)

The accumulation of Aβ peptides (deposits are primarily composed of two isoforms of amyloid-beta (Aβ): Aβ40 and Aβ42, The peptide A42 is considered the most toxic.) create the insoluble structures that define histopathologically the AD (senile plaques) that causes neuronal toxicity leading to neurodegeneration and end up with neuronal death (Paroni et *al*., 2019).

3.2. Tau protein and neurofibrillary tangles (NFTs)

Tau is a microtubule-associated protein that is vital for preserving microtubule stability and integrity playing an essential role in proper cell function and nutrient transport in neurons (Moloney et *al*., 2021).

Neurofibrillary tangles are the result of a form of tau protein that is abnormally hyperphosphorylated and aggregated (Fig. 2). The presence of NFTs and microtubule dissociation cause deterioration of axonal transport mitochondrial and cytoskeletal impairment, oxidative stress, neuroinflammation and synapses damage (H. Br et *al*., 2010).

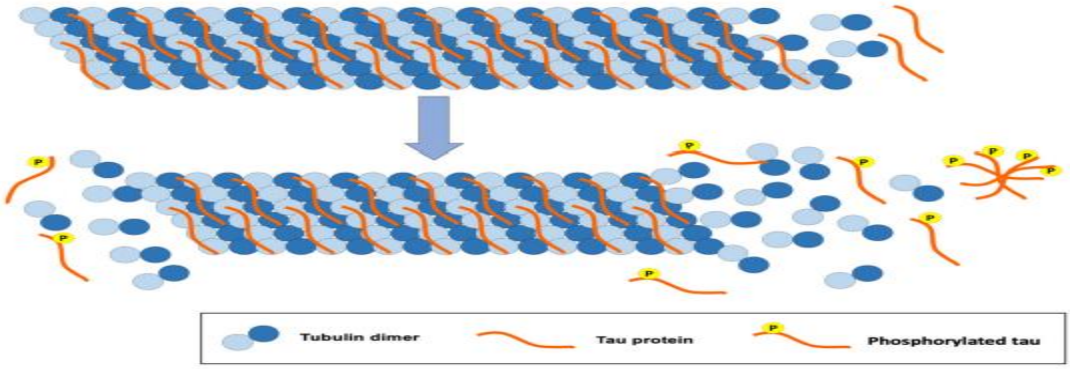

Figure 2. Consequences of tau protein hyperphosphorylation for the structure of tubulin microtubules, a classic pathology of AD (García-Morales et *al*., 2021)

4. Clinical stages of Alzheimer's disease

4.1. Mild stage

This stage is characterized by mild cognitive decline such as mood changes, slight memory loss and speech difficulties. In this stage, individuals are often asymptomatic (Ozben & Ozben, 2019).

4.2. Moderate stage

As the disease worsens, different cortical functions are changed causing difficulties in executive ability of daily living. In spite of these cognitive impairments, these people still engage in work, interact with others and live independently (Joe & Ringman, 2019).

4.3. Severe stage

In the severe (late) stage AD patients suffer from serious memory loss, psychomotor difficulty, confusion, noticeable linguistic abnormalities, causing important changes for the family members who take on the role of caregivers (Di Resta & Ferrari, 2019).

Chapter 2

Diagnostic Approaches for Alzheimer's Disease

1. Diagnostic approaches for Alzheimer's disease

Accurate and timely diagnosis of Alzheimer's disease is critical to providing effective care, managing clinical symptoms, and guiding the development of specific treatment strategies. Diagnostic approaches typically combine clinical assessments, cognitive evaluations, and advanced neuroimaging techniques (Assunção et *al*., 2022).

1.1. Clinical assessment and cognitive screening

1.1.1. Cognitive and neuropsychological testing

Cognitive and neuropsychological tests play a vital role in the diagnosis of Alzheimer's disease. They are designed to assess key cognitive domains such as memory, attention, language abilities, and executive functioning. Commonly used cognitive tests for Alzheimer's disease include the Mini-Mental State Examination (MMSE), Montreal Cognitive Assessment (MoCA), Activities of Daily Living (IADL), Minnesota Multiphasic Personality Inventory (MMPI), Five-Word Memory Test, and Clock Drawing Test (CDT) (Harvey, 2019).

1.2. Neuroimaging techniques

1.2.1. Structural magnetic resonance imaging (sMRI)

Magnetic resonance imaging (MRI) is a non-invasive imaging method that uses magnetic fields and radio waves to produce high-resolution images of the anatomical structures of the brain (Fig. 3) (Vemuri & Jack, 2010).

Magnetic resonance imaging studies show that atrophy of the hippocampus and medial hippocampal cortex occurs in the early stages of Alzheimer's disease, followed by degeneration of the temporal, parietal, and neocortical regions. This pattern of brain volume loss is valuable for early diagnosis and monitoring the progression from mild cognitive impairment (MCI) to Alzheimer's disease (Devanand et *al*., 2007).

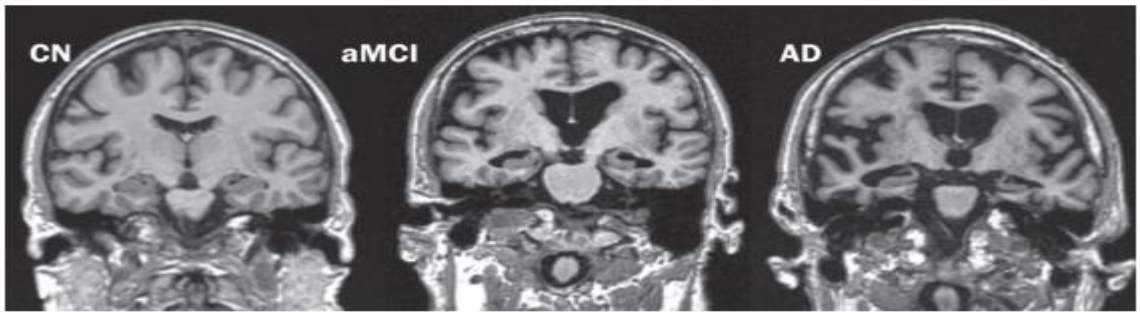

Figure 3. Progressive medial temporal lobe atrophy in a cognitively normal elderly person (CN), a patient with amnesic mild cognitive impairment (aMCI), and a patient with Alzheimer's disease (AD) (Vemuri & Jack, 2010)

1.2.2. Positron emission tomography (PET)

Positron emission tomography (PET) involves introducing a radioactive substance into the bloodstream that selectively binds to specific molecular targets in the brain. When the radioactive substance emits positrons, their detection enables the generation of three-dimensional images that depict their distribution. In Alzheimer's disease, PET is used to identify beta-amyloid (Aβ) plaques, tau pathology, glucose metabolism, and neuroinflammation. Radioactive substances are often designed to bind to specific proteins of interest; for example, Pittsburgh compound B ([^{11}C]PIB) targets beta-amyloid plaques, while several fluorine-18-labeled (^{18}F) radioactive substances have also been developed to image beta-amyloid (Fig. 4) (G et al., 2022).

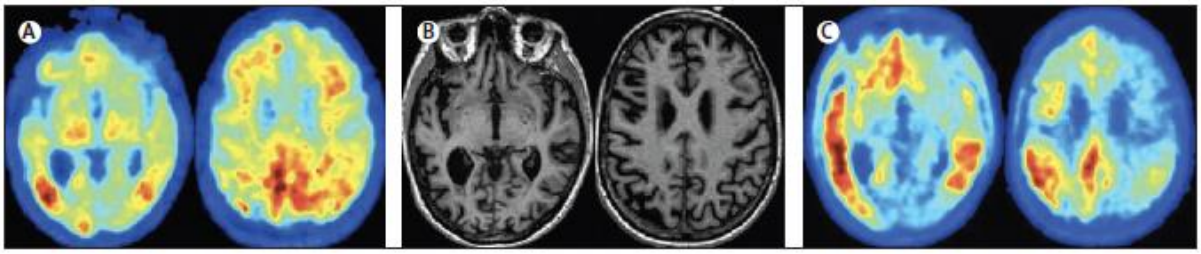

Figure 4. Multimodal Neuroimaging of Amyloid and Tau Pathology (Scheltens et *al*., 2021)

A. Amyloid PET imaging using Pittsburgh compound B reveals predominant amyloid accumulation in the posterior cingulate cortex.

B. T1-weighted MRI shows generalized cortical atrophy in both hemispheres.

C. PET scan for tau using the tracer AV1451 indicates tau deposition primarily in the inferior temporal lobe and left parietal lobe, with mild involvement of the posterior cingulate region (Scheltens et *al*., 2021).

1.2.3. Computed Tomography (CT)

Computed tomography (CT) scans show characteristic findings of advanced Alzheimer's disease, including diffuse brain atrophy, ventricle enlargement, and cortical sulcus dilation. CT also plays a crucial role in the differential diagnosis of dementia, helping to rule out other possible causes (Fig. 5) (Varghese et *al*., 2013).

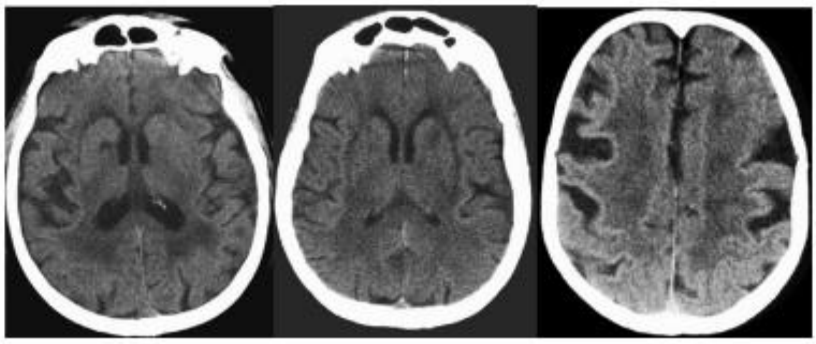

Figure 5. CT scan of mixed dementia shows prominent cortical atrophy along with vascular changes, including white matter changes and sinusoidal infarcts (P. M et *al*., 2011)

1.3. Biomarkers

Biomarkers are quantifiable indicators that provide valuable insights into the presence, progression, and underlying causes of a disease. In Alzheimer's disease, these markers are essential for improving diagnostic accuracy, tracking disease progression, and evaluating treatment effectiveness. Biomarkers associated with Alzheimer's disease are generally classified into categories such as cerebrospinal fluid (CSF) markers and blood-based biomarkers (Fig. 6) (Cummings, 2019).

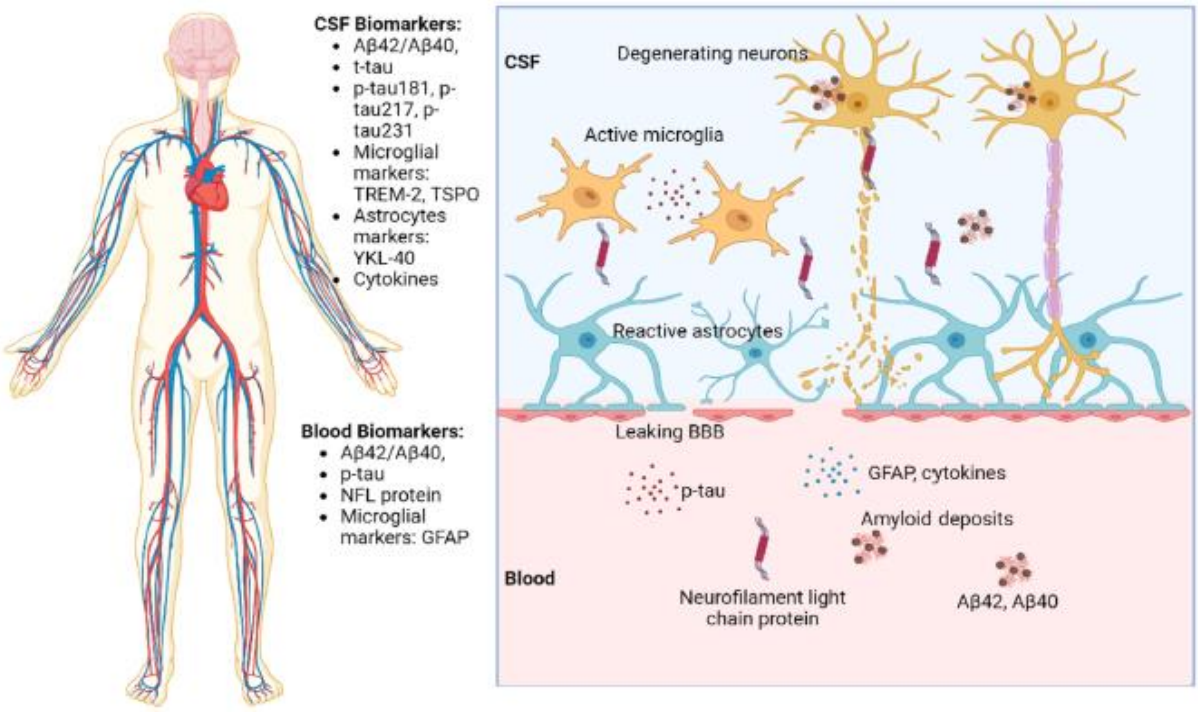

Figure 6. Blood and CSF biomarkers for Alzheimer's disease (Kamatham et *al*., 2024)

Despite significant advances in medical research, the antemortem diagnosis of Alzheimer's disease remains an ongoing challenge for the scientific community. This is largely due to its reliance on clinical criteria, which can complicate distinguishing Alzheimer's from other neurodegenerative disorders. According to many scientists, the definitive diagnosis of Alzheimer's disease is made through an autopsy of the brain of a patient who likely died from the disease (Cr et *al*., 2018).

Section II

Experimental Section

Chapter 3

Materials and Methods

1. Objective of the study

The study aims to identify the most important factors, diseases, and disorders associated with Alzheimer's disease before the onset of the disease, and to attempt to understand why certain factors are more prevalent than others by explaining this correlation statistically and biologically, and how these factors can be considered potential risk factors that contribute to the onset and progression of Alzheimer's disease.

The study idea is based on the hypothesis that the following factors (age 65 years or older, sex distribution, hypertension, diabetes, and a family history of Alzheimer's disease) exist in higher proportions than other factors: (e.g. thyroid disorder, heart disease, hypercholesterolemia, psychological and neuropsychiatric disorders, respiratory, digestive, musculoskeletal diseases, etc.)

2. Description of the study

It is a retrospective study conducted on a cohort of 250 patients diagnosed with Alzheimer’s disease, whose medical records were collected from the years 2022 to 2025. The data were obtained from the Memory and Cognitive Remediation Unit (Fig. 7, 8) of the Neurology Department at the University Hospital Center of Blida, Algeria. This unit represents the nation’s sole specialized center dedicated to the care, diagnosis, and longitudinal follow-up of patients with Alzheimer’s disease and related dementias. As a national reference center, it provides a comprehensive and centralized source of clinical data, thereby offering a unique opportunity to investigate the demographic, clinical, and comorbid characteristics associated with Alzheimer’s disease in the Algerian population.

Algeria has approximately 200,000 people with Alzheimer's disease, according to a 2019 Ministry of Health report.

Figure 7. Memory and cognitive remediation unit (University Hospital Center of Blida)

Figure 8. Memory and cognitive remediation unit (University Hospital Center of Blida)

- **Inclusion criteria**

Confirmed diagnosis of Alzheimer's disease based on internationally recognized diagnostic criteria (which will be explained)

Availability of complete medical records.

- **Exclusion criteria**

Diagnosis of non-Alzheimer's dementia (e.g., vascular dementia, frontotemporal dementia, Lewy body dementia).

Incomplete or missing clinical data.

3. Data collection

Data were retrospectively extracted from the archived and medical records of the Memory and Cognitive Remediation Unit. A standardized data extraction form (It is attached in the annex part) was used to ensure consistency across patient files.

4. Data processing and analysis

Data were collected from data extraction form and processed using Excel 2013.

Chapter 4

Results and Discussion

1. Distribution of patients according to non-modifiable risk factors

1.1. Distribution of patients by age

The percentage of those with AD aged 65 years and over is 79.2% with a total of 198 individuals.

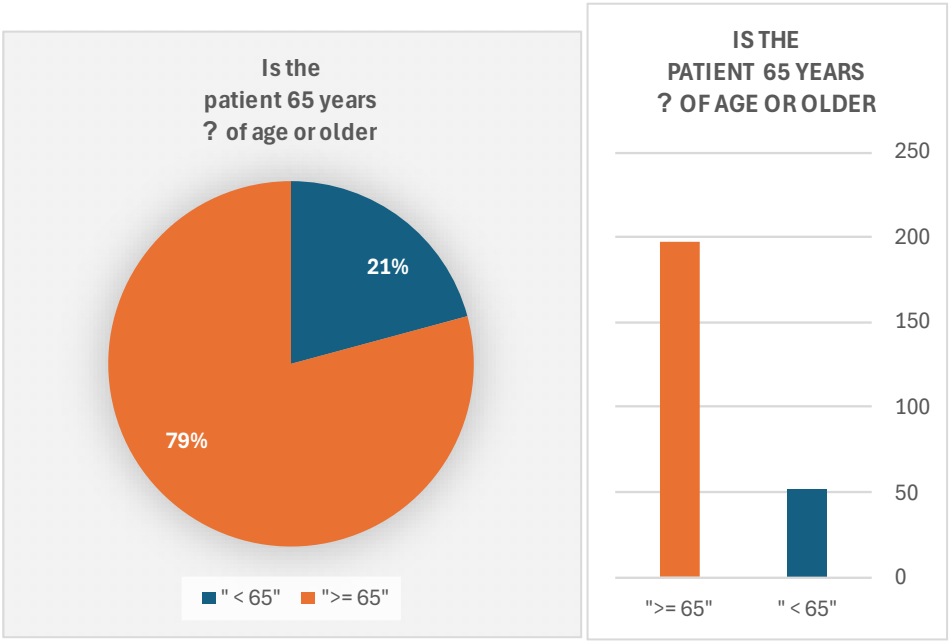

Figure 9. Distribution of patients by age

This percentage, in terms of its association with the onset of Alzheimer's disease, is largely consistent with scientific facts and studies that have proven that advancing age is the primary and main risk factor for the onset of Alzheimer's disease.

An example of these studies is what Mathuranah et *al*., (2012) cunducted (Mathuranath et *al*., 2012).

The study began with an initial sample of 1066 individuals aged 55 years or older who were cognitively normal at baseline. Over an average follow-up period of 8.1 years, 104 participants developed dementia. Of these, 98 were diagnosed with Alzheimer's disease (AD), indicating that AD accounted for approximately 94% of all new dementia cases in this cohort.

According to Mathuranah et *al*., (2012)

Incidence Rates by Age Group

- ✓ For individuals aged ≥55 years:

Incidence of AD: 11.67 cases per 1,000 person-years

Confidence Interval (CI): 10.9 – 12.4

Interpretation: On average, for every 1,000 people over 55, about 11–12 develop AD each year.

✓ For individuals aged ≥65 years:

Incidence of AD: 15.54 per 1,000 person-years

CI: 14.6 – 16.5

The incidence is higher among older adults, consistent with age being a strong risk factor.

Mathuranah et *al*., (2012) Found The incidence of AD increased significantly and proportionately with age: Age is a strong and consistent risk factor. As age increases, the likelihood of developing AD rises substantially, reinforcing the need for age-targeted interventions.

Through the percentage of people aged 65 years and older obtained from Alzheimer's patient medical records (79%) and according to Mathuranah et *al*., (2012) age is a major risk factor for the development of Alzheimer's disease.

1.1.1. Ageing as a risk factor for neurodegenerative disease (physiopathological mechanisms)

Aging is a gradual, complex process that impacts all organs and cellular systems, driven by interconnected biological events over time. It follows a sequential progression regulated by distinct molecular pathways activated at various stages. This leads to a steady decline in physiological functions (Fig. 10), increasing vulnerability to disease and risk of death (Riedel et *al*., 2016).

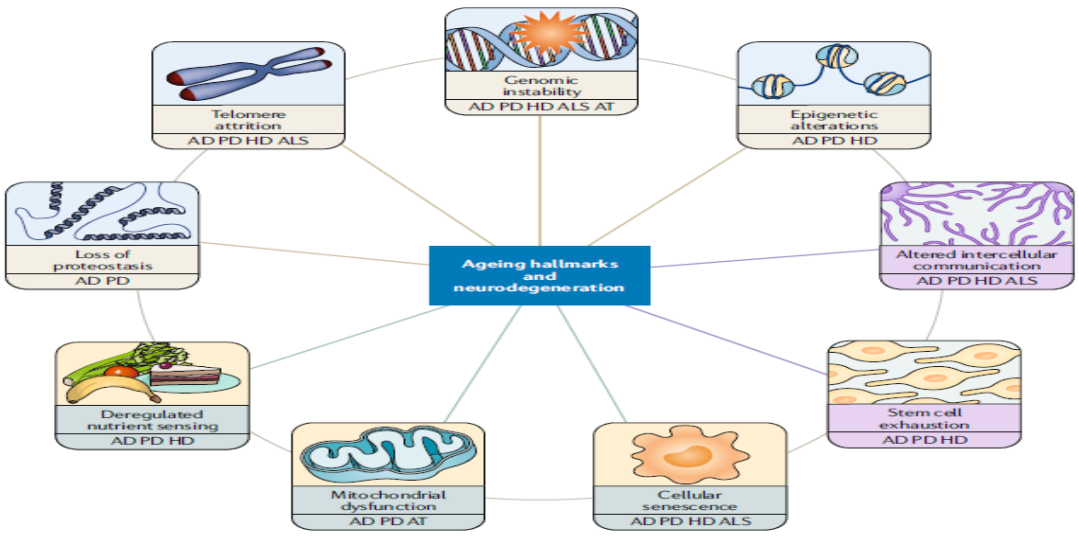

Figure 10. Hallmarks of ageing (Hou et *al*., 2019)

1.2.1.1. Genomic instability and DNA damage

Various forms of DNA damage such as bulky additives, non-base sites, single-strand and double-strand breaks, base mismatches, as well as insertions and deletions, are associated with the development and progression of neurodegeneration (Jeppesen et *al*., 2011).

Oxidative DNA damage caused by endogenous reactive oxygen species (ROS) can promote inflammation, accelerate aging, and increase the risk of cancer and neurodegenerative diseases (Thanan et *al*., 2014).

1.2.1.2. Telomere attrition

Telomeres are DNA-protein structures at chromosome ends that shorten with each cell division, unless maintained by telomerase or other mechanisms. This shortening contributes to cellular and potentially organismal aging. Impaired telomere maintenance has been shown to accelerate aging in both mice and humans (López-Otín et *al*., 2013).

1.2.1.3. Epigenetic alterations

Epigenetic modifications-such as DNA and histone methylation, barylation, and acetylation-affect the chromatin's tertiary structure and regulate its functions, including transcription and DNA replication. Age-related changes in these epigenetic marks are increasingly linked to the development of neurodegenerative diseases (Bradley-Whitman & Lovell, 2013).

1.2.1.4. Loss of proteostasis

Proteostasis refers to the balance between protein synthesis and degradation, maintained in eukaryotic cells by the proteasome system, autophagy pathway, ubiquitin machinery, and lysosomal system. Ubiquitin-tagged proteins are marked for degradation, while autophagy clears misfolded proteins and damaged organelles, helping reduce inflammation. Disruptions in proteostasis, including protein misfolding and aggregation, are key features of many neurodegenerative diseases (Tanaka & Matsuda, 2014).

1.2.1.5. Mitochondrial dysfunction and mitophagy

Neurons have high energy demands and are particularly vulnerable to mitochondrial dysfunction. When mitochondria fail to function properly, reactive oxygen species (ROS)

production increases, promoting both normal aging and the development of neurodegenerative diseases (Johri & Beal, 2012).

In addition to ATP production, mitochondria play essential roles in multiple cellular pathways, including apoptosis, calcium signaling, and lipid synthesis. All of these are key factors in the development of neurodegenerative diseases. Mitochondrial function in the brain declines with age and is considered an important and early driver of the aging process (Keogh & Chinnery, 2015).

1.2.1.6. Cellular senescence

Cellular senescence is a biological process in which cells permanently lose their ability to divide and reproduce, usually in response to various stressors or damage. While it acts as a protective mechanism against cancer and tissue damage in the short term, it plays an important and complex role in aging (Kültz, 2005).

Processes potentially involved in cellular senescence include: chronic DNA damage response (DDR), senescence-associated secretory phenotype (SASP), cell cycle arrest, impaired autophagy, oxidative stress and inflammation (Bhatia-Dey et *al*., 2016).

1.2.1.7. Deregulated nutrient sensing and altered metabolism

Key nutrient sensing pathways and molecules include insulin, insulin-like growth factor 1 (IGF-1), mechanistic target of rapamycin (mTOR), AMP-activated protein kinase (AMPK), and sirtuins (López-Otín et *al*., 2013).

Metabolic dysfunction is commonly observed in individuals with neurological disorders and may be associated with low NAD^+ levels, mitochondrial dysfunction, and elevated oxidative stress (Babbar & Sheikh, 2013).

1.2.1.8. Stem cell exhaustion

Functional stem cells are essential for maintaining health during aging. However, their ability to regenerate and proliferate declines as an organism ages. This decline is attributed to various age-related factors, including increased DNA damage, decreased efficiency of DNA repair mechanisms, impaired protein homeostasis, gene dysregulation, mitochondrial dysfunction, telomerase inactivation, and the onset of cellular senescence (Oh et *al*., 2014).

1.2.1.9. Altered intercellular communication and immune function

Changes in hormone levels, such as leptin, ghrelin, insulin, adiponectin, and IGF-1, play a regulatory role in neuronal damage and the progression of neurodegeneration. The immune system is also essential for brain development, and since both the nervous and immune systems undergo age-related changes, dysregulation of immune responses in the brain is likely a contributing factor to neurodegenerative processes (Amor & Woodroofe, 2014).

1.2. Distribution of patients by sex

The percentage of women with AD is 52.80% with a total of 132 individuals, and the percentage of men is 47.20 with a total of 132 individuals.

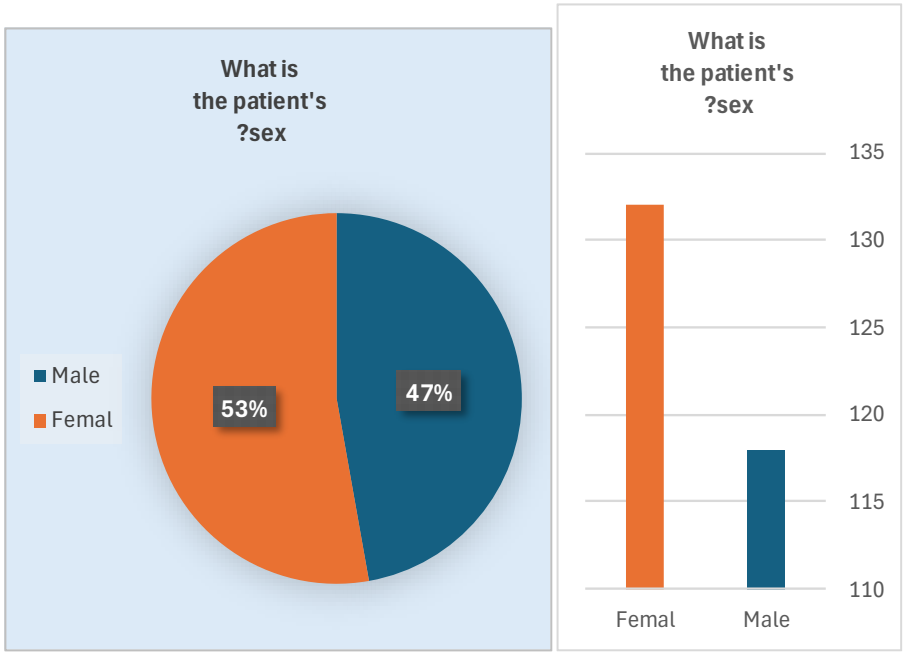

Figure 11. Distribution of patients by sex

That is, the percentage of women with Alzheimer's disease is slightly higher than that of men. This percentage is somewhat lower than studies that estimate the percentage of women at risk of Alzheimer's disease at around 60%. This may be due to the number of samples and files filtering, but it remains higher among women.

Studies and research on the relationship between sex and the onset of dementia and Alzheimer's disease (although limited) indicate that Alzheimer's disease appears in women approximately two-thirds more often than in men. Even among those with Alzheimer's disease,

the severity of symptoms is more severe in women than in men, both in terms of the apparent external symptoms and the internal molecular disturbances.

Gong et *al*., (2023) conducted a meta-analysis of individual participant data, including 29,850 individuals (58% female) from 21 cohorts spanning six continents. Using mixed-effects Cox regression models, the researchers calculated sex-specific hazard ratios and hazard ratios between women and men to assess the associations between risk factors and multi-cause dementia (Gong et *al*., 2023).

The analysis included 29,850 eligible participants (58% women) without dementia at study entry, drawn from 21 studies conducted in 18 countries across six continents. Over a median follow-up period of 4.6 years (range 0.01–19.6 years), 2089 cases of multi-cause dementia were identified, 66% of whom were women. Specifically, 1442 cases were recorded among 16744 participants in Western countries (8.6%), 306 cases among 8031 participants in Asian countries (3.8%), and 341 cases among 5075 participants in other regions (6.7%).

The mean baseline age of participants was 71.6 years, ranging from 24 to 120 years, with a mean age of 72.0 years for women and 71.0 years for men.

Gong et *al*., (2023) found on a global scale, women had a 12% higher risk of developing all-cause dementia compared to men. Specifically, the hazard ratio (HR) for women was 1.12, with a 95% confidence interval (CI) ranging from 1.02 to 1.23, indicating a statistically significant increased risk relative to men, who served as the reference group.

When the analysis was stratified by economic region, the disparity was even more pronounced in low- and lower-middle-income countries (LMICs). In these settings, women exposed a 73% higher risk of dementia compared to men, with a hazard ratio of 1.73 (95% CI: 1.25–2.39). This finding underscores a substantial gender-based difference in dementia risk within economically disadvantaged populations.

According to Gong et *al*., (2023) women face a greater risk of developing dementia from all causes, both globally and particularly in low- and middle-income countries was concluded by Gong et *al*.,2023.

This is another study that investigated sex difference in Alzheimer's disease (AD) and other brain pathologies conducted by (Oveisgharan et *al*., 2018).

Postmortem data from 1453 individuals enrolled in two longitudinal community-based studies of aging, the Religious Orders Study and the Rush Memory and Aging Project. Comprehensive postmortem neurological assessments were performed to identify a range of

brain pathologies, including Alzheimer's disease, neocortical Lewy bodies, TAR DNA-binding protein 43 (TDP-43), hippocampal sclerosis, as well as gross and microinfarcts, atherosclerosis, arteriosclerosis, and cerebral amyloid angiopathy.

According to Oveisgharan et *al*., (2018) women showed significantly higher overall Alzheimer's pathology scores than men (Estimate = 0.102, SE = 0.022, $p < 0.001$), roughly equivalent to 12 years of additional aging in men. Tau tangle density was also higher in women (Estimate = 0.334, SE = 0.074, $p < 0.001$), matching levels seen in men 13 years older.

Amyloid-β load was slightly higher in women. It was marginally significant in the basic model (Estimate = 0.124, SE = 0.065, $p = 0.056$), but became statistically significant after cohort adjustment (Estimate = 0.139, SE = 0.064, $p = 0.031$).

Women had higher odds of pathologic AD diagnosis (OR = 1.35, 95% CI: 1.06–1.72, $p < 0.001$) and more severe arteriolosclerosis (OR = 1.28, 95% CI: 1.04–1.58, $p = 0.018$). In contrast, they were less likely to have large infarcts (OR = 0.78, 95% CI: 0.61–0.98, $p = 0.037$), although this was reduced after risk adjustment.

The study of Oveisgharan et *al*., (2018) provides strong evidence that women exhibit more severe neuropathology associated with Alzheimer's disease than men, particularly in terms of tau tangle density and overall Alzheimer's disease burden. These differences persist even after accounting for age, education, and other potential confounding factors.

According to the women Through the percentage of women with Alzheimer's disease, which is higher than the percentage of men in the examined medical records (53%, 47% respectively) which it is one of the most important factors associated with Alzheimer's patients and the results of Gong et al., (2023) and Oveisgharan et *al*., (2018) women are more susceptible to Alzheimer's disease than men.

1.2.1. Understanding why women have more Alzheimer’s disease than men

About two-thirds of people diagnosed with Alzheimer's-related dementia are women, and women have a higher lifetime risk of developing Alzheimer's-related dementia (1 in 5) than men (1 in 10) (Plassman et *al*., 2007).

The prevalence of Alzheimer's disease is expected to rise significantly among women compared to men in the coming years, a trend attributed to women's longer life expectancy and underlying biological factors (Hebert et *al*., 2013).

Sex-specific risk factors for women

Longevity

Some suggest that sex differences in Alzheimer's disease are mainly due to women's longer life expectancy, as the risk of Alzheimer's increases with age. However, while evidence remains mixed on whether women are inherently at higher risk, a growing body of research supports this idea, indicating that factors beyond longevity may also contribute to the observed disparity (Mielke et *al*., 2014).

Biology

A. Hormones

Estrogen is believed to have neuroprotective effects and is thought to act through several mechanisms such as promoting the growth and maintenance of cholinergic neurons, enhancing cholinergic activity, exhibiting antioxidant properties, and influencing alternative pathways of amyloid metabolism (Janicki & Schupf, 2010).

After menopause, the dominant form of estrogen shifts from the potent 17β-estradiol to the weaker estrone. Emerging evidence indicates that while 17β-estradiol may support cognitive function, estrone could have more harmful effects (Galea et *al*., 2017).

B. Pregnancy

Pregnancy and its complications may contribute to cognitive decline in women later in life. For example, a history of preeclampsia has been linked to an increased risk of mild cognitive impairment and dementia in later life. Furthermore, pregnancy and motherhood involve a wide range of biological and social changes, some of which may influence the risk of dementia through mechanisms that are not yet fully understood (Fields et *al*., 2017).

C. Brain structure and function

Structurally, males generally exhibit larger total brain volumes and a greater proportion of white matter, while females tend to have a higher relative amount of gray matter matter (Cosgrove et *al*., 2007).

Females tend to have greater blood flow and neural connectivity in the parietal association cortex, while males show higher activity in the motor and visual cortex. These differences may affect the risk and progression speed of cognitive decline and dementia. (Hsieh et *al*., 2012).

A brain autopsy study found that women accumulate more Alzheimer's disease markers, especially neurofibrillary tangles, and these changes are more closely linked to dementia symptoms in women than in men (Barnes et *al*., 2005).

Sociocultural risk factors

A. Education

Low education is linked to a greater risk of Alzheimer's dementia in both sexes, but because women have historically had less access to education, they bear a disproportionately higher burden of dementia related to poor education (Russ et *al*., 2013).

B. Exercise

Midlife physical activity lowers Alzheimer's risk, but women are generally less active than men, partly due to parenting duties. Additionally, exercise's cognitive benefits may depend on estradiol levels and menopause, being stronger when estrogen is higher (Rovio et *al*., 2005).

Psychiatric co-morbidities

A. Depression

Depression, which women are twice as likely to experience as men, is a risk factor for Alzheimer's disease. Early-life depression may increase dementia risk later, while late-life depression can signal early cognitive decline. Longer duration of depression is linked to higher Alzheimer's risk (Rl et *al*., 2006).

B. Insomnia

Insomnia, which is more common in women, may increase the risk of faster cognitive decline and Alzheimer's disease. Adequate sleep is crucial for memory, and studies show people with insomnia are twice as likely to develop cognitive issues. However, it's unclear if insomnia directly raises Alzheimer's risk or if this is linked to stress and depression (Cricco et *al*., 2001).

1.3. Distribution of patients according to family history

The most important of these relationships are first-degree relatives with Alzheimer's disease. Other relationships are just a bit more detail.

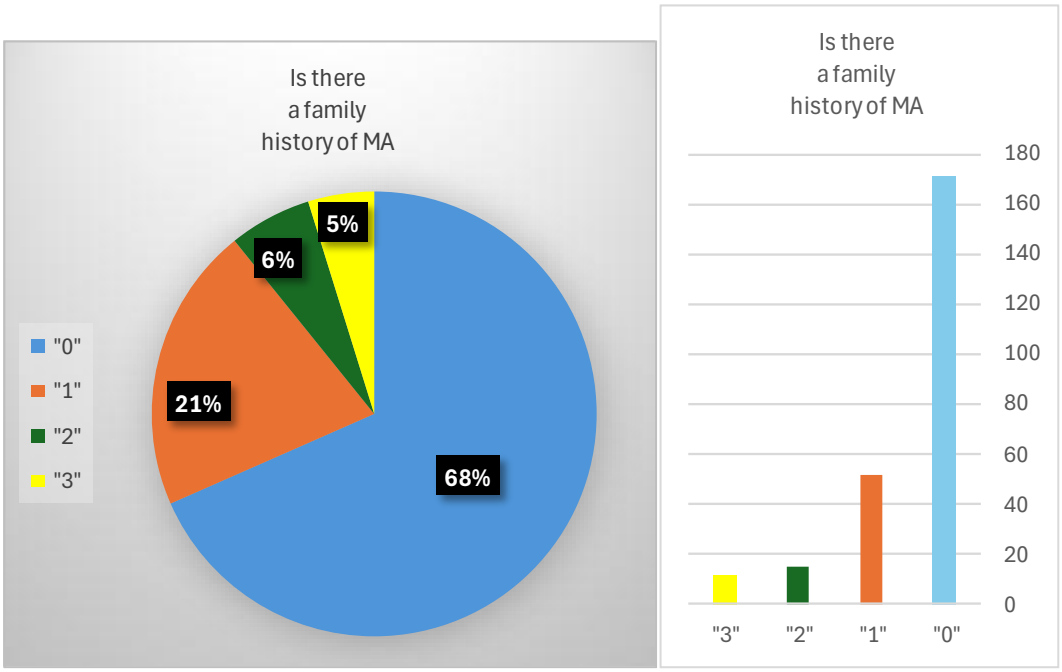

Figure 12. Distribution of patients according to family history

0 means there are no relatives with Alzheimer's disease: percentage of 68.40% with a total of 171 individuals.

1 means there is at least one first-degree relative with Alzheimer's disease: percentage of 20.80% with a total of 52 individuals.

2 means there is at least one second-degree relative with Alzheimer's disease: percentage of 06.00% with a total of 15 individuals.

3 means there is at least one first-degree relative and at least one second-degree relative with Alzheimer's disease: percentage of 04.80% with a total of 12 individuals.

Here we see that the family history of Alzheimer's disease is among the factors associated with the onset of Alzheimer's disease.

This is consistent with studies, research and scientific interpretations that consider a family history of Alzheimer's disease to be among the factors contributing to the onset of Alzheimer's disease.

In order to understand the nature of the relationship between family history and Alzheimer's disease, we begin with a comprehensive study that extends to the extended family, including first-degree relatives, second-degree relatives, and even third-degree relatives in a detailed analysis conducted by Cannon-Abright et *al*., (2019) (Cannon-Albright et *al*., 2019).

Cannon-Abright et *al*., (2019) utilized data from the Utah Population Database (UPDB), which integrated detailed genealogical, demographic, and health records. It focused on 1.3 million individuals with well-documented family histories (at least 12 of 14 direct ancestors known) to ensure reliable relationship data. These records were linked to Utah death certificates from 1904 to 2014, which included causes of death coded using ICD revisions 6–10. And included individuals with extensive ancestry data and Utah death certificates listing Alzheimer's disease (AD), identified by ICD-9 code 331.0 and ICD-10 codes F00 and G30. A total of 270,818 individuals were analyzed to estimate AD rates, using class-specific rates stratified by sex, birth year range, and birthplace. These rates reflect patterns within the UPDB population, enabling valid statistical comparisons.

According to Cannon-Abright et *al*., (2019) The analysis included 270818 individuals with detailed genealogical records and Utah death certificates; among them, 4436 had Alzheimer's disease (AD) listed as the cause of death. Most AD deaths (3,298) occurred after 2000, with 64% being women and a median age at death of 85. Only 1.5% of deaths occurred before age 65, while 25% occurred after age 89. On average, AD cases had 4.2 first-degree, 6.7 second-degree, and 18.5 third-degree relative availability for analysis with linked genealogical and death certificate data.

Cannon-Abright et *al*., (2019) found:

- First-degree relatives (FDRs):

Having ≥1 FDR with AD is associated with a significantly elevated AD risk:

RR = 1.73 (95% CI: 1.59–1.87, $p < 0.00001$)

Risk increases with more affected FDRs:

FDR ≥2: RR = 3.98 (very high), CI: 3.26–4.82

FDR ≥3: RR = 6.24 (CI: 2.48–12.46)

FDR ≥4: RR = 14.77 (CI: 5.42–21.15) -indicating a very strong familial aggregation.

- Second-degree relatives (SDRs):

When FDRs and TDRs are ignored, the presence of ≥1 SDR with AD is also associated with increased risk:

RR = 1.06, modest but statistically significant ($p < 0.00001$)

SDR ≥2: RR = 1.25 (not significant, p = 0.23)

SDR ≥3 or ≥4: Risk increases further and becomes significant (RR up to 2.69)

When controlling FDR and TDR, SDRs still show:

≥1 SDR: RR = 1.51 (CI: 1.37–1.66)

≥2 SDRs: RR = 2.04 (CI: 1.48–2.74)

- Third-degree relatives (TDRs)

TDRs alone (FDR = 0 and SDR = 0) show a small but statistically significant increase in AD risk:

≥2 TDRs: RR = 1.17 (CI: 1.07–1.29)

≥3 TDRs: RR = 1.43 (CI: 1.21–1.68)

≥4 TDRs: RR = 1.44 (CI: 1.05–1.93)

≥1 TDR only does not significantly increase risk (RR = 0.99, p = 0.70)

Cannon-Abright et *al*., (2019) concluded that a major predictor of increased AD risk is family history, especially among first-degree relatives. The strongest correlation is found with several impacted FDRs.

Moderate risk is increased by second-degree relatives, particularly when there are no impacted FDRs.

When present in larger numbers, third-degree relatives raise risk in a statistically significant but smaller way.

Another study analyzed the influence of family history of dementia in the development and progression of late-onset Alzheimer's disease made by (Scarabino et *al*., 2016). The study included 420 community-dwelling patients with sporadic late-onset Alzheimer's disease (AD) (mean age: 77.0 ± 7.8 years; 67.9% women), diagnosed according to DSM-IV and NINCDS-ADRDA criteria. All patients lacked a Mendelian inheritance pattern and were not screened for APP, PSEN1, or PSEN2 mutations. The control group consisted of 109 unrelated individuals without dementia (mostly spouses; mean age: 71.3 ± 9.1 years; 60.6% women).

All participants were white and from northern Italy (Verona/Veneto). The family history of dementia was gathered via interviews with patients, caregivers, and relatives. Detailed information on relationship degree and affected relatives was available for 57% of Alzheimer's patients. Family history data are likely more accurate for Alzheimer's patients than controls, due to better disease awareness in their families.

Scarabino et *al*., (2016) found that family history (FH) is a significant risk factor for Alzheimer's Disease (AD):

13.8% of controls reported a family history of dementia (FH+), whereas a much higher proportion of AD patients did -this difference was highly statistically significant (P = 0.0002).

The crude odds ratio (OR) of 2.87 means that individuals with a family history of dementia were nearly 3 times more likely to have AD compared to those without such a history (95% CI: 1.6–5.1).

Patients with FH+ AD had a higher frequency of the APOE ε4 allele (49.6%) than those with FH− AD (38.9%); this difference was statistically significant (P = 0.04), indicating that APOE ε4 may have a stronger role in family instances.

Among controls, there were no significant differences between those with and without a family history in terms of age, sex, or APOE ε4 frequency, suggesting that these variables did not influence the control group comparison.

The results strongly support that family history is an important independent risk factor for Alzheimer's disease, and that APOE ε4 increases the risk even further, especially among those with a positive family history.

- To determine whether the effect of family history (FH) on the risk of Alzheimer's disease (AD) depends on the presence of the APOE ε4 allele, a known genetic risk factor for AD, Scarabino et *al*., (2016) divided the sample (n = 529) into APOE ε4 carriers and non-carriers.

In both groups, FH was a significant and independent risk factor for AD:

- Non-carriers of APOE ε4 (n = 323):

FH increased AD risk with an odds ratio (OR) of 2.5 (95% CI: 1.2–4.9, P = 0.009).

- Carriers of APOE ε4 (n = 197):

FH conferred an even higher AD risk with an OR of 3.7 (95% CI: 1.04–12.9, P = 0.03).

Scarabino et *al*., (2016) Concluded that family history significantly increases AD risk regardless of APOE ε4 status.

The risk is additive: individuals with both a positive FH and APOE ε4 allele are at particularly elevated risk.

This supports the view that familial aggregation of AD cannot be fully explained by APOE ε4 alone, and that other genetic or shared environmental factors likely contribute.

Through the percentage of family history obtained from Alzheimer's patient medical records (21%), which classified family history as one of the most factors associated with Alzheimer's disease, and according to Cannon-Abright et *al*., (2019) and Scarabino et *al*., (2016) family history is a contributing risk factor in the development of Alzheimer's disease.

1.3.1. Explication of how family history contributes to AD risk

A family history of Alzheimer's is a major risk factor, typically due to multiple genetic variants that individually have small effects but collectively raise the risk significantly (Loy et *al*., 2014).

1.3.1. The role of genetics

A. Early-onset familial AD (EOFAD): Rare but highly genetic

APP (amyloid precursor protein), PSEN1 (presenilin 1), and PSEN2 (presenilin 2) are important autosomal dominant genes.

Mechanism

Mutations in these genes increase the production of beta-amyloid (Aβ) or impair its clearance. Aβ peptides aggregate to form amyloid plaques, a hallmark of Alzheimer's disease. Presenilin proteins are part of the γ-secretase complex, which cleaves the APP protein. Mutations affect the cleavage site, favoring the toxic Aβ 42 protein. These mutations are highly penetrant: if a parent carries one, their offspring have a 50% chance of inheriting it (Karch & Goate, 2015).

B. Late-onset AD (LOAD): Polygenic and sporadic

The most common form (after age 65) (Pierce et *al*., 2017). A family history increases the risk even without Mendelian mutations.

APOE ε4 allele (Apolipoprotein E gene):

The strongest known risk factor for sporadic AD, one copy increases the risk by about three-fold: two copies by about 8-12-fold. It encodes a lipid transfer protein, which is important in cholesterol metabolism and clearance of beta-amyloid protein.

Mechanism

APOE ε4 causes:

Increased Aβ aggregation and impaired clearance.

Tau pathology (neurofibrillary tangles) is promoted.

both mitochondrial malfunction and synaptic toxicity.

Neuroinflammation by activation of microglia (T. Br et *al*., 2022).

Other polygenic contributors

Genome-wide association studies (GWAS) have identified dozens of genes involved in:

Innate immunity (e.g., TREM2, CR1)

Endocytosis and lysosomal pathways (e.g., BIN1 and PICALM)

Cholesterol transport (e.g., ABCA7) (Kamboh et *al*., 2012).

1.3.2. Epigenetic and molecular pathways in inherited risk

Gene expressions related to AD risk may be influenced by epigenetic modifications inherited from previous generations, even in the absence of monogenic mutations:

Epigenetic mechanisms:

DNA methylation: Modifies the expression of genes related to AD, such as MAPT (which codes for tau) or APP.

Histone alterations: Impact transcription and chromatin structure.

Non-coding RNAs (microRNAs, for example): Control amyloid metabolism and synaptic activity.

These factors are influenced by environmental exposures in parents and grandparents (such as stress, diet, and toxins) and can make offspring more susceptible to Alzheimer's disease through altered neuroplasticity (Balazs, 2014)**.**

1.3.3. Pathophysiological impact

Effects of inherited molecular changes:

Activation of the amyloid cascade: Excessive accumulation of beta-42 leads to synaptic damage.

Hyperphosphorylation of tau: Promotes the formation of intracellular neurofibrillary tangles.

Neuroinflammation: Chronic activation of microglia leads to neuronal damage.

Oxidative stress and mitochondrial dysfunction: Impair neuronal energy metabolism.

Synapse loss and brain atrophy: Lead to progressive cognitive decline (T. Br et *al*., 2022)**.**

The following figure (Fig. 13) shows the different genes and how they affect the development of Alzheimer's disease.

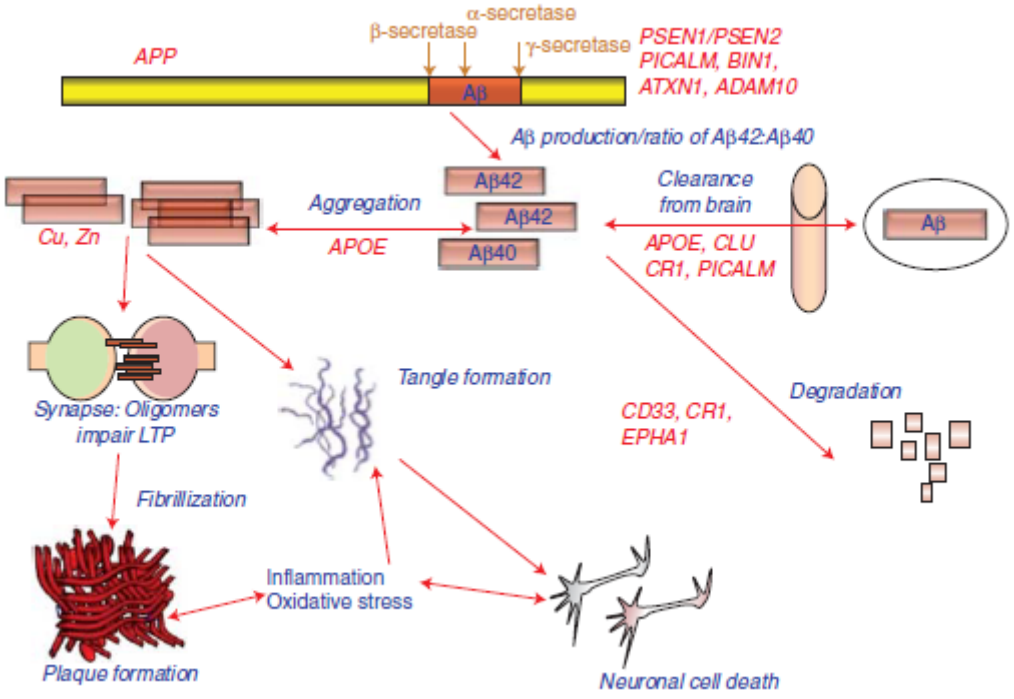

Figure 13. Potential roles of some Alzheimer's disease (AD) genes in the pathogenesis of Aβ associated Alzheimer's disease (Tanzi, 2012)

2. Distribution of patients according to modifiable risk factors

2.1 Distribution of patients by high blood pressure

The percentage of people with high blood pressure among Alzheimer's patients is 48.80% with a total of 122 individuals.

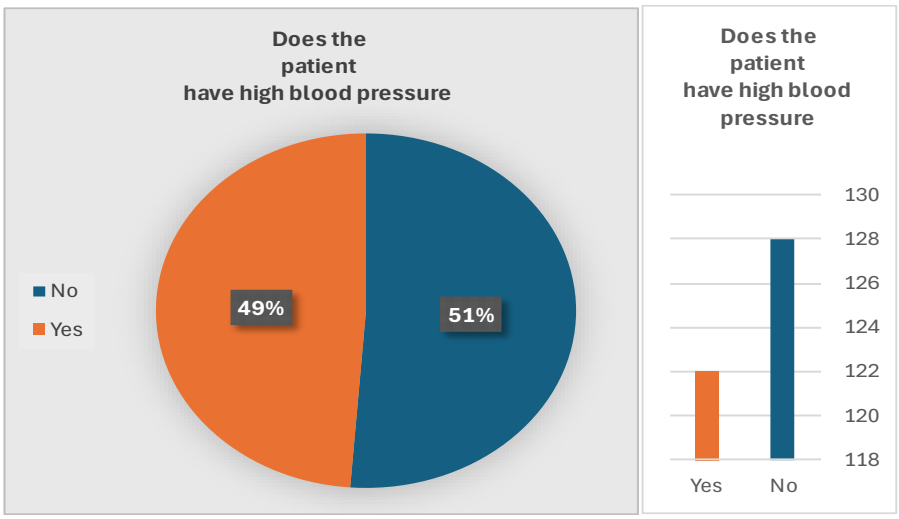

Figure 14. Distribution of patients by high blood pressure

Here, high blood pressure or hypertension appears to be one of the primary modifiable factors associated with the onset of Alzheimer's disease.

Numerous research studies have proven that high blood pressure is one of the most important modifiable risk factors contributing to the development of Alzheimer's disease.

Wu et *al*. (2003) conducted an epidemiological study on the relationship between high blood pressure and Alzheimer's disease, analyzing blood pressure changes before and after disease onset. The study included 16488 participants from a dietary trial (1984–1991), with 301 later diagnosed with Alzheimer's based on DSM-IV criteria (Wu et *al*., 2003).

The researchers categorized participants by their blood pressure levels (high, borderline, normal, low) to compare Alzheimer's prevalence and tracked blood pressure changes in patients before and after disease onset. They used multiple logistic regression to evaluate high blood pressure as an independent risk factor and conducted a trend test to examine the dose-response relationship between blood pressure and Alzheimer's risk.

According to Wu et *al*., (2003):

High blood pressure was found to be a risk factor for AD by multiple logistic regression (OR = 1.97, 95% CI: 1.09–3.54, P = 0.02).

This is a multivariate analysis using logistic regression, which:

estimates the odds of developing Alzheimer's disease in people with high blood pressure compared to those without.

Adjusts for other confounding variables (such as age, sex, and education)

- Odds ratio (OR = 1.97):

This means that people with high blood pressure have about twice the odds (97% higher) of developing Alzheimer's disease compared to those with normal or low blood pressure.

- 95% Confidence Interval (1.09–3.54):

The "true" odds ratio is 95% likely to lie between 1.09 and 3.54, Since this range does not include 1.0, the result is statistically significant.

- P-value = 0.02:

This confirms statistical significance, because $P < 0.05$.

Reserchers reject the null hypothesis (no association) and conclude that high blood pressure is associated with an increased risk of developing Alzheimer's disease.

- High blood pressure is an independent risk factor for Alzheimer's, according to this adjusted evidence by Wu et *al*., (2003).

Trend test showed that there is a significant dose-response relationship between blood pressure and AD ($P < 0.0002$):

The dose-response relationship means that as blood pressure rises, the risk of Alzheimer's disease also gradually increases. The trend test statistically confirms this gradual association.

The very small P value ($P < 0.0002$) strongly supports this relationship as highly statistically significant.

Wu et *al*., (2003) found that it's not just a binary relationship (high blood pressure versus no high blood pressure) but rather a spectrum: the higher the blood pressure, the greater the risk of developing Alzheimer's disease, even within the high blood pressure category. And provide multi-level evidence linking high blood pressure to an increased risk of Alzheimer's disease.

Another study conducted by McGrath et *al*., (2017) to assess whether blood pressure from midlife (40–64 years) to late life (≥65 years) is associated with the risk of developing dementia (McGrath et *al*., 2017).

Researchers followed 1440 dementia-free participants (53% women, mean age 55) from the Framingham-Freshspring cohort over five examinations from midlife (1983–1987) to late life (1998–2001), with an average 8-year follow-up for dementia. It examined the impact of various blood pressure patterns—including midlife and late-life hypertension, low late-life blood pressure, persistent hypertension, and significant BP decline—on dementia risk. During follow-up, 107 participants (7.4%) developed dementia, including 81 with Alzheimer's. The average midlife blood pressure was 127/80 mmHg, and 27% had midlife hypertension.

According to McGrath et *al*., (2017):

- Midlife Blood Pressure and Dementia

  Multivariable Analysis Result

- ✓ Midlife systolic hypertension was associated with an increased risk of incident dementia:

  Hazard Ratio (HR) = 1.57

  95% Confidence Interval (CI) = 1.05–2.35

- ✓ Dose–response relationship:

  For every 10 mmHg increase in midlife systolic blood pressure (SBP):

  HR = 1.17

  95% CI = 1.05–1.31

  - HR = 1.57 (for midlife systolic hypertension):

Individuals with high systolic blood pressure in midlife (≥140 mm Hg) had a 57% higher risk of developing dementia later in life compared to those with normal systolic blood pressure, after adjusting for other factors (multivariate analysis).

Because the 95% CI (1.05–2.35) does not include 1.0, this result is statistically significant, indicating a true association.

- HR = 1.17 per 10 mmHg increase in SBP:

There is a linear/dose-response effect: every 10 mmHg increase in systolic blood pressure in midlife increases the risk of dementia by 17%.

Again, the 95% confidence interval (1.05–1.31) excludes the value 1.0, confirming statistical significance.

McGrath et *al*., (2017) found high systolic blood pressure in midlife is an important and independent risk factor for dementia later in life. The existence of a dose-response relationship strengthens the evidence for a causal or contributory relationship, underscoring the importance of managing high blood pressure in midlife for long-term brain health.

- ➢ Mid-to late life BP and dementia
- ✓ Persistent Systolic Hypertension from Mid- to Late Life

HR for Dementia = 1.96 (95% CI: 1.25–3.09)

HR for Alzheimer's Disease (AD) = 1.73 (95% CI: 1.02–2.94)

Individuals with persistent high systolic blood pressure from middle to late life were nearly twice as likely to develop dementia and 73% more likely to develop Alzheimer's disease than those without persistent high blood pressure. Confidence intervals do not include 1.0, so both associations are statistically significant. Concluded by McGrath et *al*., (2017).

- ✓ Higher Cumulative Burden of SBP (AUC measure)

HR = 1.27 per standard deviation (SD) increase

95% CI = 1.05–1.53

Increasing cumulative exposure to high systolic blood pressure (measured by area under the curve, AUC) over an 18-year period was associated with a 27% increased risk of dementia for each unit increase in SD (standard deviation). This shows that total BP burden over time-not just individual measurements-matters. The result is statistically significant. McGrath et *al*., (2017) concluded.

- ✓ Steep Decline in SBP from Mid- to Late Life

HR for Dementia = 1.63 (95% CI: 1.08–2.46)

HR for AD = 1.47 (95% CI: 0.91–2.37)

A steep decline in systolic blood pressure (slope <-0.5 vs. ≥0.5 mmHg/year) from mid- to late-life was associated with a 63% increased risk of overall dementia. However, the association with Alzheimer's disease was not statistically significant (confidence interval included 1.0). This suggests that steep declines in blood pressure may be associated with dementia other than Alzheimer's disease or reflect early systemic decline. McGrath et *al*., (2017) found.

- ✓ Interaction Between Midlife Hypertension and Steep SBP Decline

Among those who did not have high blood pressure in midlife and experienced a sharp drop in systolic blood pressure, the risk increased:

Dementia HR = 2.40 (95% CI: 1.39–4.15)

AD HR = 2.12 (95% CI: 1.12–4.00)

P for interaction = 0.023

According to McGrath et *al*., (2017): there is a significant interaction: People who did not have high blood pressure in midlife but later experienced a severe drop in systolic blood pressure were 2–2.4 times more likely to develop dementia and Alzheimer's disease. This suggests that severe blood pressure decline in normotensive individuals may be a marker of or contribute to neurodegeneration, possibly reflecting vascular fragility, cerebral ischemia, or autonomic changes associated with preclinical dementia.

McGrath et *al*., (2017) found:

Persistent elevated systolic blood pressure and the cumulative burden of blood pressure from mid- to late life significantly increase the risk of dementia.

A sharp drop in systolic blood pressure, especially in people without prior hypertension, is also associated with an increased risk of dementia, suggesting a complex dynamic between vascular aging and neurodegeneration.

Through the percentage of high blood pressure obtained from Alzheimer's patient medical records (49%), which classified high blood pressure as one of the most factors associated with Alzheimer's disease, and according to Wu et al., (2003) and McGrath et *al*., (2017), high blood pressure is a contributing risk factor in the development of Alzheimer's disease.

Studies proving the opposite are limited and have not been able to conclusively prove the absence of a relationship between high blood pressure and AD within the study's parameters. As an example, this study conducted by Legdeur et *al*., (2023) which aimed to determine whether physical, vascular, or brain pathology markers-indicative of increased vulnerability-

modify the association between blood pressure (BP) and cognitive performance in individuals aged 90 years and older (Legdeur et *al*., 2023).

Study sample: 122 participants (mean age 92.4 years) from the EMIF-AD 90+ study, including 84 individuals without cognitive impairment and 38 with cognitive impairment.

Analysis: Cross-sectional associations between blood pressure and cognitive performance were analyzed, with interaction terms to assess modification by the aforementioned markers.

According to Legdeur et *al*., (2023):

Blood Pressure (BP) Measures

Systolic BP: $\beta = 0.03$ (95% CI: -0.09 to 0.16)

Diastolic BP: $\beta = -0.02$ (95% CI: -0.14 to 0.10)

Data from the EMIF-AD 90+ study indicate that:

There is no significant cross-sectional association between blood pressure (systolic or diastolic) and cognitive performance in people aged 90 years or older.

The β coefficients (effect sizes) are very small and the confidence intervals include zero, which statistically means that no reliable effect of BP on cognition was detected in this group.

Legdeur et *al*., (2023) found that high blood pressure is not a risk factor for Alzheimer's disease in general.

2.1.1. Physiopathological mechanisms that explain how high blood pressure contributes to the onset and development of Alzheimer's disease

The central nervous system receives 20% of the total cardiac output and relies on a complex vascular network not only to deliver nutrients but also to regulate nervous homeostasis (Quaegebeur et *al*., 2011).

A. Age-related maladaptation (Age-related autoregulatory dysfunction)

In young cerebral arteries, hypertension triggers a 20-HETE-TRPC6 pathway in vascular smooth muscle cells, strengthening vessel contraction to protect brain microvessels by extending autoregulation to higher pressures. In aging arteries, this adaptive response is impaired, weakening vessel constriction and cerebral blood flow regulation. Consequently, increased blood pressure damages fragile brain microvessels, breaking down the blood-brain barrier. This leakage activates microglia, causing inflammation and releasing harmful molecules that contribute to neuronal damage and synaptic dysfunction (Toth et *al*., 2013).

B. Small vessel disease

High blood pressure and aging contribute to microvascular damage, affecting the extracellular matrix (ECM), smooth muscle cells, endothelial cells, and perivascular cells. This damage leads to microvascular rupture, rarefaction, thrombosis, impaired vasodilation, and blood-brain barrier dysfunction, ultimately leading to cerebral ischemia and neuroinflammation (Fig 24) (Girouard et *al*., 2007).

These pathological changes appear on MRI as microhemorrhages, lacunar infarcts, and white matter lesions (Fig. 15) (Jorgensen et *al*., 2018).

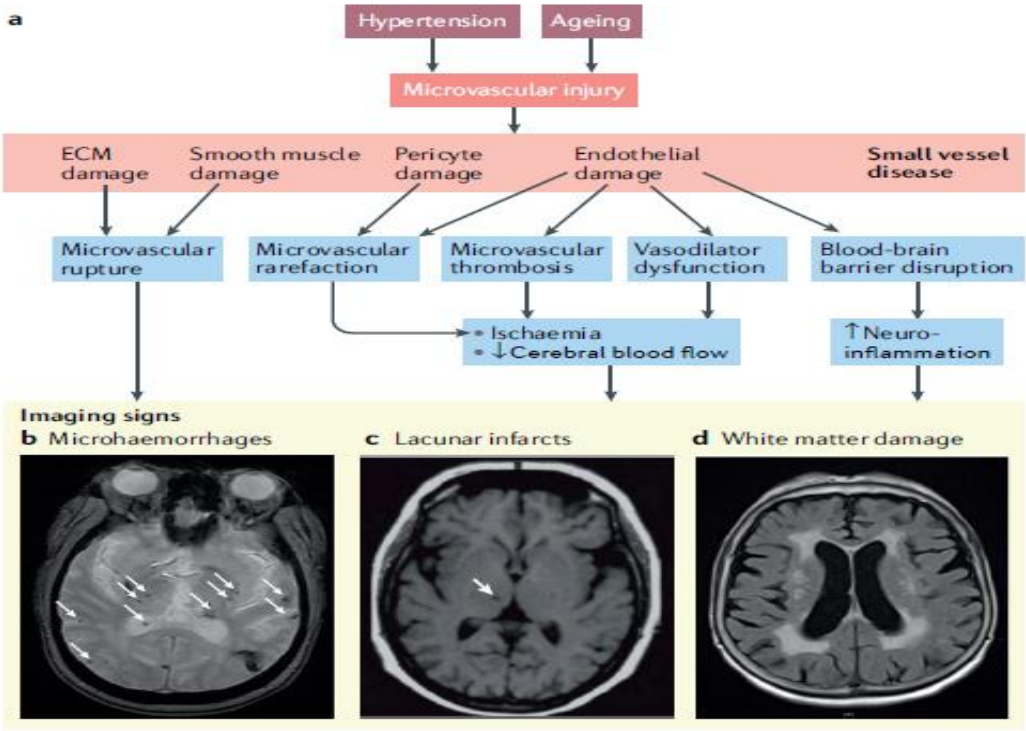

Figure 15. Hypertension-induced small vessel pathology and its radiological features (Jorgensen et *al*., 2018)

C. hypertension-induced blood–brain barrier disruption

High intraluminal pressure in cerebral microvessels increases ROS production, causing oxidative stress that damages endothelial cells and pericytes, and activates MMPs. This disrupts tight junctions and degrades the extracellular matrix, weakening the blood-brain barrier (BBB). The resulting BBB leakage triggers microglial activation, synaptic dysfunction, and myelin damage. Hypertension-related inflammation further worsens synaptic and white matter injury (Zhang et *al*., 2010).

D. Oxidative stress and cellular resilience

The transmission of elevated blood pressure to the fragile distal parts of the cerebral microcirculation is a major factor in microvascular injury in the elderly. This elevated pressure increases vascular wall tension and mechanical dilation, inducing oxidative stress in endothelial cells and vascular smooth muscle cells (VSMCs) through the activation and increased production of NADPH oxidases and increased production of reactive oxygen species (ROS) in mitochondria. With aging, this pressure-induced oxidative stress is exacerbated by a decreased ability of cells to withstand hemodynamic and oxidative challenges (Springo et *al*., 2015).

2.2. Distribution of patients by diabetes mellitus

The percentage of people with diabetes mellitus among Alzheimer's patients is 29.20% with a total of 73 individuals.

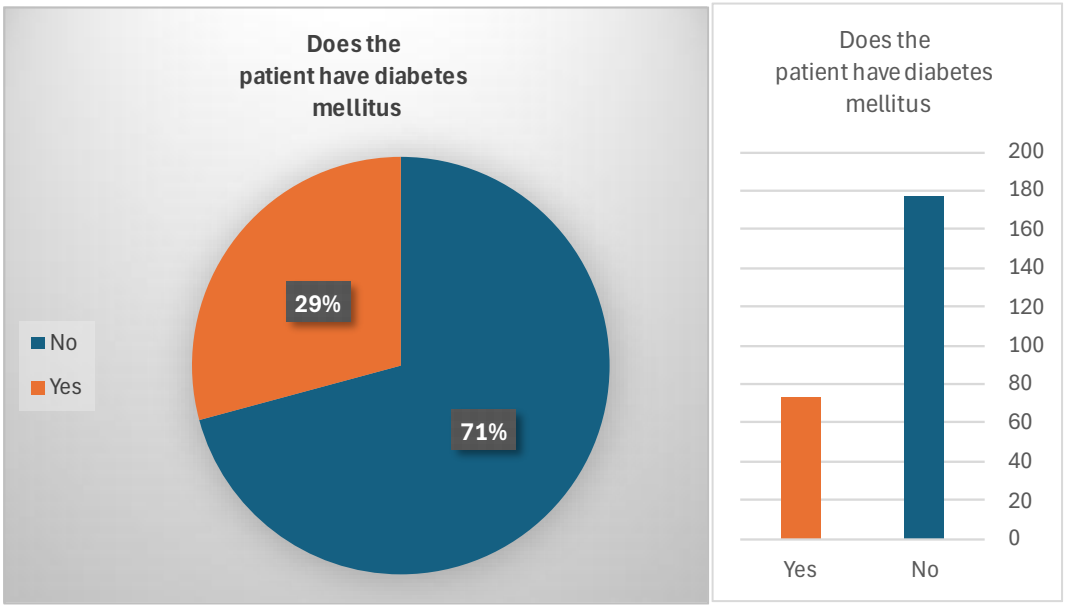

Figure 16. Distribution of patients by diabetes mellitus

This indicates that diabetes is also an important factor associated with Alzheimer's disease. Many studies indicate that diabetes is among the important modifiable risk factors contributing to the development of Alzheimer's disease.

To determine whether diabetes mellitus (DM) is associated with:

Increased risk of Alzheimer's disease (AD)

Declining cognitive function in various areas

Arvanitakis Z. et *al*., (2004) conducted a Longitudinal cohort study (Z et *al*., 2004).

This study followed 847 dementia-free elderly Catholic nuns, priests, and brothers from the Religious Orders Study for a median of 5.5 years. Participants received annual clinical assessments, consented to brain donation, and were monitored for diabetes and cognitive function. Analyses adjusted for age, sex, and education.

Of the 127 participants with diabetes, 85 (66.9%) were taking medication, including 15 taking insulin only, 55 taking oral hypoglycemic agents only, and 15 taking both. Therefore, most participants with diabetes were receiving medication.

According to Arvanitakis Z. et *al*., (2004):

- ✓ Prevalence of Diabetes in the Study Sample

  127 of the 824 participants (15.4%) developed diabetes at some point during the study.

  91 participants (11.0%) developed diabetes at study's baseline.

- ✓ Alzheimer's Disease Incidence and its Association with Diabetes

  151 participants (18.3%) developed Alzheimer's disease during the follow-up period.

  31 of these individuals (151 individuals) (20.5%) developed diabetes.

  Hazard Ratio for AD with Diabetes

  HR = 1.65

  95% Confidence Interval: 1.10–2.47

Individuals with diabetes were 65% more likely to develop Alzheimer's disease than those without diabetes, even after adjusting for age, sex, and education.

The confidence interval (1.10–2.47) does not include the value 1, indicating that this result is statistically significant.

This supports the hypothesis that diabetes is an independent risk factor for Alzheimer's disease.

Arvanitakis Z. et *al*., (2004) found that Diabetes is associated with a significantly increased risk of Alzheimer's disease in older adults. This association persists even after adjusting for important factors such as age, sex, and education.

To understand this relationship more deeply, a more comprehensive study was conducted by Huang et *al*., (2014) this study aims to clarify the debated link between diabetes mellitus (DM) and Alzheimer's disease (AD) by analyzing a nationwide, population-based dataset to examine whether DM is associated with an increased risk of developing AD (Huang et *al*., 2014).

Researchers analyzed data from the Taiwan National Health Insurance Research Database, identifying 71433 individuals newly diagnosed with diabetes (mean age 58.7) since January 1997. Using propensity score matching, they were paired with 71311 non-diabetic individuals based on demographic and medical history factors. Participants were followed until December 31, 2007, with Alzheimer's disease as the primary outcome.

According to Huang et *al*., (2014):

Over a follow-up period of up to 11 years (mean duration: 5.56 ± 3.1 years), 346 individuals with diabetes (0.48%) were diagnosed with Alzheimer's disease, compared with 266 individuals without diabetes (0.37%).

- The results of the Kaplan-Meier analysis show that individuals with diabetes had a significantly higher incidence of Alzheimer's disease compared to those without diabetes, as confirmed by the log-rank test ($p < 0.001$).

People with diabetes develop Alzheimer's disease at a higher rate and speed than those without the disease. The difference between the two groups is real and statistically significant, not random.

- To identify diabetes mellitus as an independent predictor of Alzheimer's disease risk, Cox proportional hazards regression analysis was performed:
  - Diabetes mellitus was associated with a 76% increased risk of AD (HR = 1.76; 95% CI: 1.50–2.07; $p < 0.001$), establishing it as a strong independent predictor.

Huang et al., (2014) concluded that diabetes is an independent risk factor for Alzheimer's disease.

- To assess whether both type 1 and type 2 diabetes independently increase the risk of Alzheimer's disease (AD):

  The analysis of diabetes subtypes by Huang et al., (2014) showed that both Type 1 and Type 2 diabetes were significantly associated with an increased risk of Alzheimer's disease (AD):

- Patients with Type 1 diabetes (n = 2,791) had an 89% higher risk of developing AD (HR = 1.89; 95% CI: 1.23–2.89; $p = 0.004$), indicating a statistically significant association.
- Type 2 diabetes, observed in a larger group of 68,462 patients, was also linked to a 57% increased risk of AD (HR = 1.57; 95% CI: 1.34–1.85; $p < 0.001$), confirming a highly significant relationship.

Through the percentage of diabetes mellitus obtained from medical records of Alzheimer's patient (29%), which classified diabetes mellitus as one of the most factors

associated with Alzheimer's disease, and according to Arvanitakis Z. et *al*., (2004) and Huang et al., (2014), diabetes mellitus is a contributing risk factor in the development of Alzheimer's disease.

Studies proving that diabetes is not a risk factor for Alzheimer's disease are limited. For example, this prospective community-based cohort study conducted by Akomolafe et *al*., (2006) to evaluate and contrast the likelihood of developing Alzheimer's disease between individuals with diabetes mellitus and those without (Akomolafe et *al*., 2006).

Study Design: Prospective cohort study using the Framingham Original Cohort.

The Framingham Study was a prospective study of 2210 dementia-free participants (mean age 70 ± 7 years, 60% women) from the original Framingham cohort.

According to Akomolafe et *al*., (2006):

At baseline, 202 participants (9.1%) had diabetes. During follow-up (mean 12.7 years; range 1–20 years), 17 of the 202 participants with diabetes (8.4%) and 220 of the 2008 participants without diabetes (11.0%) developed Alzheimer's disease.

In the unadjusted or subgroup analysis, individuals with diabetes had nearly three times the risk of developing Alzheimer's disease (AD) compared to non-diabetics (RR = 2.98; 95% CI: 1.06–8.39; p = 0.03), indicating a statistically significant association. However, in the main adjusted analysis of the full cohort, the association between diabetes and AD was not statistically significant (RR = 1.15; 95% CI: 0.65–2.05; p not significant), as the confidence interval included 1.0, suggesting no reliable difference in AD risk after controlling for confounding factors.

Akomolafe et *al*., (2006) found that while one result (relative hazard ratio = 2.98) indicates a significant association between diabetes and an increased risk of Alzheimer's disease, the main or fully adjusted result (relative hazard ratio = 1.15) shows no statistically significant association. Therefore, the overall conclusion of the study is that there is no strong or consistent evidence linking diabetes to Alzheimer's disease in the general population.

2.2.1. Physiopathological mechanisms that explain how diabetes mellitus contributes to the onset and development of Alzheimer's disease

Type 2 diabetes (T2DM) and Alzheimer's disease (AD) are both age-related conditions, and research over the past 20 years shows that having T2DM increases the risk of developing AD (Sims-Robinson et *al*., 2010).

2.2.1.1. Impaired insulin signaling

Insulin resistance results from a weakened response of cells to insulin stimulation, leading to compensatory insulin oversecretion, resulting in hyperinsulinemia. This elevated insulin level is associated with disruption and impairment of various functions of the central nervous system (Zhao & Townsend, 2009).

A. Hyperphosphorylation of tau protein

Peripheral hyperinsulinaemia leads to excessive insulin crossing the blood-brain barrier and activating insulin receptors in the brain. This triggers signaling pathways (PI3K-Akt, MAP kinases, etc.) that increase glycogen synthase kinase-3 (GSK-3) activity, which promotes neurodegeneration by phosphorylating tau protein (Fig. 17) (Rorbach-Dolata & Piwowar, 2019).

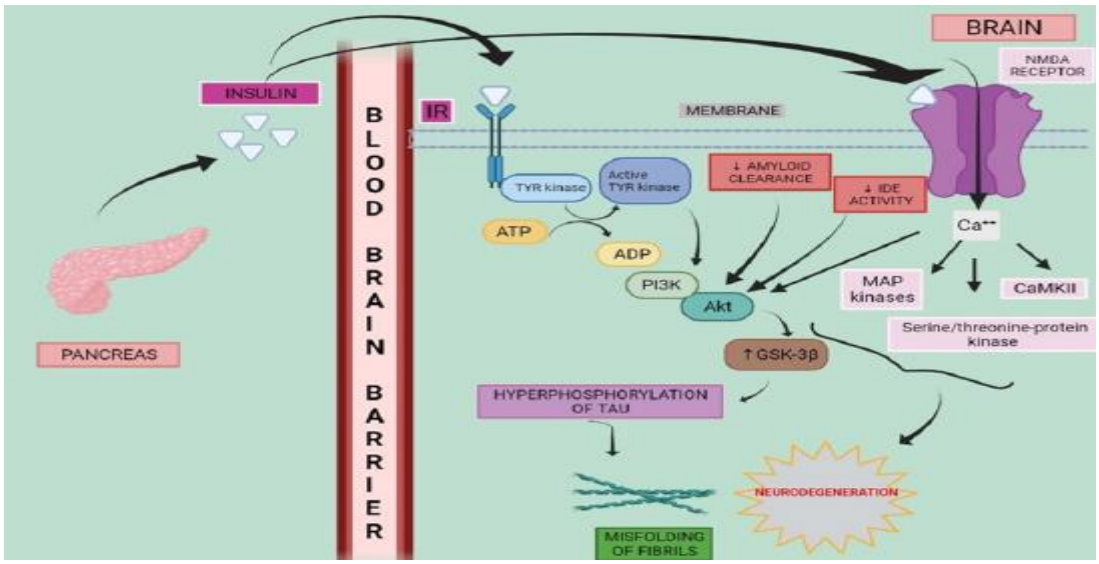

Figure 17. Insulin signaling and neurodegeneration (Patel et *al*., n.d.)

B. Oxidative stress and mitochondrial dysfunction

Hyperinsulinemia from insulin resistance increases oxidative stress, mitochondrial dysfunction, and inflammation. Insulin regulates lipid metabolism, and inflammation arises through mechanisms like NF-κB activation by AGEs and toxic ceramide production. This inflammation worsens brain insulin resistance, oxidative damage, and mitochondrial problems, promoting neurodegeneration (Butterfield et *al*., 2014).

C. DYRK1A and GSK3 enzymes

Normally, insulin inhibits GSK3β via the PI3K/Akt pathway, preventing tau hyperphosphorylation. In insulin resistance, GSK3β remains active, causing tau hyperphosphorylation. Concurrently abnormal activation of DYRK1A and GSK3β increases amyloid-β production and tau phosphorylation, leading to amyloid plaques and neurofibrillary tangles, which disrupt brain insulin signaling. In the pancreas, these enzymes impair beta cell growth and promote inflammation, reducing insulin secretion and worsening central insulin resistance and neurodegeneration (Hamzé et *al*., 2022).

3. Treatment and management of Alzheimer's disease

There is no cure for Alzheimer's disease yet. As a complex neurodegenerative disorder, treatment focuses on relieving symptoms, slowing progression, and improving quality of life. Current therapies include both drug-based and non-drug approaches, mainly targeting early-stage symptom management (Scheltens et *al*., 2016).

The figure below (Fig. 18) illustrates the methods and types of pharmacological, non-pharmacological treatments and treatments that are under research and development.

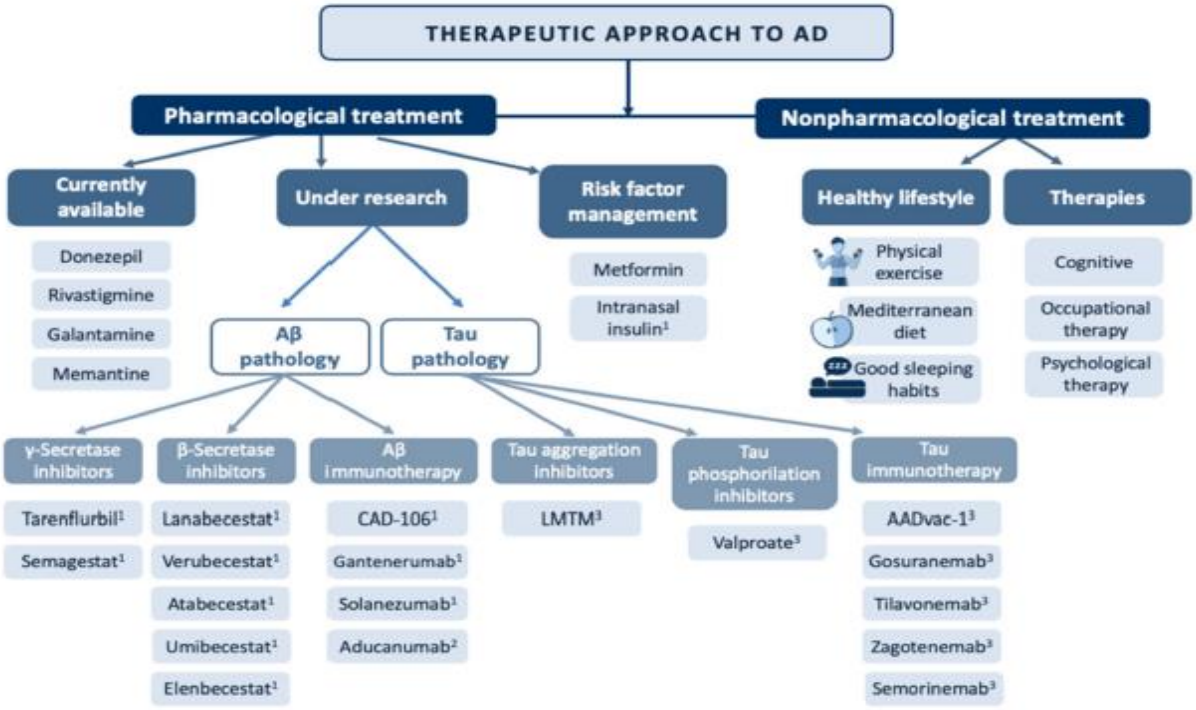

Figure 18. Key therapeutic modalities in the management of Alzheimer's disease (García-Morales et *al*., 2021)

3.1. Pharmacological Treatment

3.1.1. Currently Available Pharmacological Treatment

Acetylcholinesterase inhibitors (AChEIs) are key drugs for Alzheimer's treatment. They work by blocking acetylcholinesterase, the enzyme that breaks down acetylcholine, thereby increasing acetylcholine levels, which are typically low in Alzheimer's. Common AChEIs include donepezil, rivastigmine, and galantamine (Sharma, 2019) and Memantine (Atri et *al*., 2019).

Before starting acetylcholinesterase inhibitors (AChEIs), an electrocardiogram (ECG) is recommended because these drugs can cause sick sinus syndrome and other heart conduction problems (Briggs et *al*., 2016).

3.1.2. Pharmacological Treatment under Investigation

Therapies targeting beta-amyloid focus on three main approaches: reducing Aβ42 production using β- and γ-secretase modulators; preventing beta-amyloid plaque buildup with aggregation inhibitors or metal chelators; and enhancing beta-amyloid clearance via active or passive immunotherapy (Yiannopoulou & Papageorgiou, 2020).

The latest strategy for treating tau pathology is immunotherapy: a specific immune response against hyperphosphorylated tau protein (Congdon & Sigurdsson, 2018).

3.1.3. Risk factor management

Alzheimer's disease is influenced by multiple risk factors, notably type 2 diabetes, where central insulin resistance occurs. Enhancing insulin availability or sensitivity in the brain is a promising therapeutic strategy for Alzheimer's management (Bendlin, 2019).

Intranasal insulin therapy has been studied for Alzheimer's disease. A double-blind randomized controlled trial found that daily nasal doses of 40 IU insulin for four months improved memory in people with Alzheimer's and mild cognitive impairment (Craft et *al*., 2017).

Cardiovascular diseases-such as stroke, hypertension, high cholesterol, heart failure, and atrial fibrillation-along with risk factors like high homocysteine levels and smoking, are linked to Alzheimer's onset. Early detection and management of these cardiovascular risks may help reduce Alzheimer's incidence in older adults (de Toledo Ferraz Alves et *al*., 2010).

3.2. Non-pharmacological treatment

3.2.1. Cognitive stimulation and rehabilitation

medical treatments, healthcare professionals Besides like occupational therapists and psychologists are crucial in managing Alzheimer's disease. Occupational therapy, in particular, helps improve patient independence by supporting daily activities through cognitive and behavioral interventions (Matilla-Mora et *al*., 2016).

3.2.2. Physical exercise and lifestyle modifications

Regular physical activity benefits many body systems, including the immune, digestive, cardiovascular, and central nervous systems (Ruegsegger & Booth, 2018).

Conclusion

Conclusion

In light of the unresolved etiology of Alzheimer's disease, this study explores the most common factors associated with the condition and examines the reasons these specific factors frequently appear in both the scientific literature and clinical observations.

The results of the study were consistent with the hypothesis from which it was based, which is that the five most important factors associated with Alzheimer's patients are as follows:

Old age, 79% (198 individuals) of Alzheimer's patients are 65 years or older.

The percentage of women with Alzheimer's disease is higher than the percentage of men, women are 53% (132 individuals) and men are 47% (118 individuals)

The percentage of those who have first-degree family members with Alzheimer's disease among Alzheimer's patients is 21% (52 individuals).

The percentage of those suffering from high blood pressure among Alzheimer's patients is 49% percent (122 individuals).

The percentage of those suffering from diabetes among Alzheimer's patients is 29% (73 individuals).

According to statistical studies that examined the relationship between these factors and Alzheimer's disease, they have been statistically and biologically confirmed that these factors are the most important factors contributing to the emergence and development of Alzheimer's disease.

The results of this study confirm that Alzheimer's disease in Algeria is closely associated with several modifiable and non-modifiable risk factors, including age, sex, family history, hypertension and diabetes.

This highlights the urgent need for early screening programs, public health education on risk factor management, and improved access to geriatric care.

Future research in Algeria should focus on longitudinal studies that can better assess causality, as well as investigations of genetic and environmental interactions specific to our population.

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Annex

University Hospital Center of Blida

Patient number / Examination date:

Age: Sex:

Education Level / Occupation:

Cardiocirculatory system (Hypertension, heart failure, vascular anomalies, etc.)

……

Metabolic Diseases / Abnormalities (Diabetes, dyslipidemia, thyroid disorders, etc.)

……

Neurological diseases / Conditions (epilepsy, stroke, neuropathies, etc.)

……

Neuropsychiatric disorders / Conditions (depression, anxiety, cognitive disorders, dementia, etc.)

……

Family history (Indicate hereditary, chronic or genetic diseases in the family)

……

Surgical history

……

Allergies / Drug allergies

……

Other diseases / abnormalities / disorders (Digestive, respiratory, dermatological, musculoskeletal, etc.)

……

الخلاصة

هدفت هذه الدراسة الاستعادية الوصفية التحليلية إلى تحديد العوامل الرئيسية المرتبطة بمرض الزهايمر. تم تحليل 250 سجلاً طبياً لمرضى شُخِّصوا بمرض الزهايمر بين عامي 2022 و2025 في المستشفى الجامعي بالبليدة، الجزائر.
ووصفت الدراسة الأمراض والحالات المصاحبة لتحديد أكثر العوامل المصاحبة شيوعاً. وكشفت النتائج أن 79% من المرضى كانوا في سن 65 عاماً أو أكثر، وأن 53% منهم نساء مقابل 47% رجال، وأن 21% لديهم تاريخ عائلي من الدرجة الأولى للإصابة بمرض الزهايمر، وأن 49% منهم يعانون من ارتفاع ضغط الدم ،وأن 29% منهم مصابون بمرض السكري. بعد البحث والتحليل في دراسات مختلفة تبين أن هذه العوامل الخمسة هي أهم عوامل الخطر التي تُسهم في ظهور مرض الزهايمر وتطوره.

الكلمات المفتاحية: مرض الزهايمر، العمر، الجنس، التاريخ العائلي، ارتفاع ضغط الدم، مرض السكري

Résumé

Cette étude rétrospective descriptive et analytique visait à identifier les principaux facteurs associés à la maladie d'Alzheimer. Elle a analysé 250 dossiers médicaux de patients diagnostiqués entre 2022 et 2025 au Centre Hospitalier Universitaire de Blida, en Algérie. L'étude a examiné les maladies et affections coexistantes afin de déterminer les facteurs associés les plus courants. Les résultats ont révélé que 79 % des patients étaient âgés de 65 ans ou plus, 53 % étaient des femmes contre 47 % des hommes, 21 % avaient des antécédents familiaux de maladie d'Alzheimer au premier degré, 49 % souffraient d'hypertension artérielle et 29 % étaient diabétiques. Après recherche et analyses dans diverses études, il est apparu clairement que ces cinq facteurs sont les facteurs de risque les plus importants contribuant à l’apparition et à la progression de la maladie d’Alzheimer.

Mots-clés : maladie d'Alzheimer, âge, sexe, antécédents familiaux, hypertension artérielle, diabète

Abstract

This retrospective, descriptive and analytical study aimed to identify the main factors associated with Alzheimer's disease. It analyzed 250 medical records of patients diagnosed between 2022 and 2025 at the University Hospital of Blida, Algeria. The study examined coexisting diseases and conditions to determine the most common associated factors. The results revealed that 79% of patients were aged 65 or older, 53% were women compared to 47% men, 21% had a first-degree family history of Alzheimer's disease, 49% had high blood pressure, and 29% were diabetic. After research and analysis in various studies, it became clear that these five factors were found to be the most significant risk factors contributing to the onset and progression of Alzheimer's disease.

Keywords: Alzheimer's disease, age, sex, family history, high blood pressure, diabetes

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Faculté : Sciences de la nature et de la vie et Sciences de la Terre et de l'univers
Département : Sciences de la nature et de la vie

الجمهورية الجزائرية الديمقراطية الشعبية
وزارة التعليم العالي والبحث العلمي
جامعة محمد خيضر بسكرة
كلية: علوم الطبيعة والحياة وعلوم الأرض والكون
قسم: علوم الطبيعة والحياة

Déclaration de correction de mémoire de master 2025

Référence du mémoire N°: ...../ 2025	PV de soutenance N°: ...../ 2025

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BOUFRIOUA ABDERRAHMAN	بوفريوة عبد الرحمان

La mention التقدير	Note(./20) العلامة	L'intitulé de mémoire عنوان المذكرة
حسن	16.67/20	Retrospective descriptive and analytical study of the major factors associated with Alzheimer's disease

Déclaration etdécision de l'enseignant promoteur : تصريح وقرار الأستاذ المشرف

Déclaration :

Je soussigné (e), YAACOUB Fadjeria, (grade) MAA à l'université de BISKRA, avoir examiné intégralement ce memoire après les modifications apportées par l'étudiant.

J'atteste que :

* le document à été corrigé et il est conforme au model de la forme du département SNV
* toutes les corrections ont été faites strictement aux recommandations du jury.
* d'autres anomalies ont été corrigées

تصريح:

أنا الممضي(ة) أسفله ..... ،
(الرتبة) ..... بجامعة .....،
أصرح بأنني راجعت محتوى هذه المذكرة كليا مراجعة دقيقة وهذا بعد التصحيحات التي أجراها الطالب بعد المناقشة، وعليه
أشهد بأن :

* المذكرة تتوافق بشكلها الحالي مع النموذج المعتمد لقسم علوم الطبيعة والحياة.
* المذكرة صححت وفقا لكل توصيات لجنة المناقشة
* تم تدارك الكثير من الإختلالات المكتشفة بعد المناقشة

Décision :

Sur la base du contenu scientifique, de degré de conformité et de pourcentage des fautes linguistiques, **Je décide** que ce mémoire doit être classé sous la catégorie

قرار :

اعتمادا على درجة مطابقتها للنموذج ، على نسبة الأخطاء اللغوية وعلى المحتوى العلمي **أقرر** أن تصنف هذه المذكرة في الدرجة :

exceptionnel متميز	excellent ممتاز	très bien جيد جدا	bien حسن	ordinaire عادي	acceptable مقبول
A+	A	(B)	C	D	E

التاريخ 2025 /06/ 12

الأستاذ المشرف

إدارة القسم

مسؤول المكتبة

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