الجمهورية الجزائرية الديمقراطية الشعبية

République Algérienne Démocratique et Populaire

وزارة التعليم العالي و البحث العلمي

Ministère de l'enseignement supérieur et de la recherche scientifique

UNIVERSITÉ DES FRÈRES MENTOURI 1

Université des Frères Mentouri Constantine

جامعه االخوة منتوري قسنطينه

Faculté des Sciences de la Nature et de la Vie

كلية علوم الطبيعة والحياة

Mémoire présentée en vue de l'obtention du diplôme de Master Domaine : Sciences de la Nature et de la Vie
Filière : Sciences Biologiques
Spécialité : Immunologie Moléculaire et Cellulaire (IMC)

Risk Factors for Alzheimer's Disease: An immunopathogenesis perspective

Présentée et soutenue par : **Saci Nada** **Le 12/06/2024**

Jury d'évaluation :

Président : ZERIZER Sakina (Pr.Université des Frères Mentouri, Constantine 1).

Encadrant : AGGOUN Cherifa (MCB.Université des Frères Mentouri, Constantine 1).

Examinateur : HADDAD Souad (MAA .Université des Frères Mentouri, Constantine 1).

Remerciement

Au nom d'Allah, le Tout Miséricordieux,

Très Miséricordieux.

Je tiens à exprimer ma profonde gratitude

mon encadreur de mémoire, Dr. Aggoun Cherifa, pour son

soutien et sa guidance précieuse.

Merci aux membres du jury Professeur Zerizer et Madame Haddad pour leur lecture attentive et leurs remarques constructives, ainsi qu'à l'ensemble du corps enseignant de la faculté des sciences de la nature et de la vie, en particulier celui de la spécialité Immunologie. Enfin, je remercie sincèrement ma famille pour leur soutien indéfectible tout au long de ce parcours.

Alhamdoulillah pour toutes les bénédictions et la guidance.

Table of contents

Table of figures

Abbreviation List

Aβ Amyloid Beta

AD Alzheimer's Disease

APOE Apolipoprotein E

APOE4 Apolipoprotein E4

APP Amyloid Precursor Protein

ARDS Alcohol-Related Dementia

BACE1 β-Site Amyloid Precursor Protein Cleaving Enzyme 1

BBB Blood-Brain Barrier

bFGF Basic Fibroblast Growth Factor

CDK5 Cyclin-Dependent Kinase 5

CCL2 Chemokine (C-C motif) Ligand 2

CNS Central Nervous System

CRP C-Reactive Protein

CSF Cerebrospinal Fluid

CXCL2 Chemokine (C-X-C motif) Ligand 2

DAMPs Damage-Associated Molecular Patterns

EGF Epidermal Growth Factor

Fcγ Fc Gamma

FcγRIIb Fc Gamma Receptor IIB

GABA Gamma-Aminobutyric Acid

GLAP Glycation End Products

GMB Gut Microbiota

GSK-3β Glycogen Synthase Kinase-3β

HGF Hepatocyte Growth Factor

IBD Inflammatory Bowel Disease

IDE Insulin-Degrading Enzyme

IL Interleukin

IL-1 Interleukin-1

IL-1α Interleukin-1 Alpha

IL-1β Interleukin-1 Beta

IL-6 Interleukin-6

IL-8 Interleukin-8

IL-10 Interleukin-10

MAPK Mitogen-Activated Protein Kinase

MARK Microtubule Affinity-Regulating Kinase

MMP Matrix Metalloproteinase

MMP-1 Matrix Metalloproteinase-1

MMP-3 Matrix Metalloproteinase-3

MMP-10 Matrix Metalloproteinase-10

MMP-12 Matrix Metalloproteinase-12

MMP-13 Matrix Metalloproteinase-13

MMP-14 Matrix Metalloproteinase-14

MRI Magnetic Resonance Imaging

NLRP3 NOD-like Receptor Family Pyrin Domain Containing 3

NFTs Neurofibrillary Tangles

NF-κB Nuclear Factor kappa-light-chain-enhancer of activated B cells

NMDAR N-Methyl-D-Aspartate Receptor

NMDA N-Methyl-D-Aspartate

OMVs Outer Membrane Vesicles

PAI-1 Plasminogen Activator Inhibitor-1

PET Positron Emission Tomography

PHFs Paired Helical Filaments

PSEN1 Presenilin 1

PSEN2 Presenilin 2

RAGE Receptor for Advanced Glycation End-products

ROS Reactive Oxygen Species

SA-β-Gal Senescence-Associated Beta-Galactosidase

SASP Senescence-Associated Secretory Phenotype

SCFAs Short-Chain Fatty Acids

SPSS Statistical Package for the Social Sciences

T2DM Type 2 Diabetes Mellitus

TGF Transforming Growth Factor

TLRs Toll-Like Receptors

TREM2 Triggering Receptor Expressed on Myeloid Cells 2

TNF-α Tumor Necrosis Factor-alpha

VEGF Vascular Endothelial Growth Factor

Summary

Alzheimer's disease is a progressive neurodegenerative disorder characterized by memory loss and cognitive decline. Risk factors are characteristics or conditions that increase the likelihood of developing a disease.

We conducted a survey of 29 patients and analyzed the data using SPSS to identify significant risk factors for AD. Our analysis confirmed that age and sex significantly influence AD prevalence, with older adults and females being more affected. Midlife obesity, lower educational attainment, family history of AD, smoking, depression, and chronic stress were identified as significant risk factors. Conversely, social engagement appeared to reduce the risk of AD.

This study also highlighted the importance of oral health, as chronic gum problems were associated with higher dementia risk. Also poor sleep quality and exposure to neurotoxic chemicals, particularly pesticides were linked to increased AD risk.

Moreover diet and gut health were crucial, with unhealthy diets and inflammatory bowel disease (IBD) contributing to higher dementia prevalence.

Overall, the findings reinforce the multifactorial nature of Alzheimer's disease and the need for a holistic approach to its prevention and management. Future research should focus on these associations to develop targeted interventions.

الملخص

مرض الزهايمر هو اضطراب تنكس عصبي يتميز بفقدان الذاكرة والمعرفة. وعوامل الخطر هي الخصائص التي تزيد من احتمالية الإصابة بالمرض.

تمت هده الدراسة الاحصائية على 29 مريضًا والتي من خلالها استخدام برنامج SPSS لتحليل البيانات وتحديد عوامل الخطر المسؤولة عن الاصابة بمرض الزهايمر. أكدت التحاليل الإحصائية بأن العمر والجنس يؤثران بشكل كبير على انتشار مرض الزهايمر، حيث يكون كبار السن والإناث أكثر تأثراً. تم تحديد السمنة في منتصف العمر، وانخفاض التحصيل العلمي، والتاريخ العائلي لمرض الزهايمر، والتدخين، والاكتئاب، والإجهاد المزمن كعوامل خطر كبيرة. وعلى العكس من ذلك، يبدو أن الارتباط الاجتماعي يقلل من خطر الإصابة بمرض الزهايمر.

كدلك وجدنا ان أهمية صحة الفم، مثل مشاكل اللثة المزمنة تساعد على حدوث ارتفاع خطر الإصابة بالخرف. كما ان قلة النوم والتعرض للمواد الكيميائية السامة للأعصاب، وخاصة المبيدات الحشرية، تعمل على زيادة خطر الإصابة بمرض الزهايمر.

علاوة على دلك فان التغدية غير صحية ومرض التهاب الأمعاء تتدخل في حدوث مرض .الزهايمر.

بشكل عام، نحتاج الى منهجية للوقاية من مرض الزهايمر و دلك بالقيام بأبحاث مستقبلية لتفادي العوامل المتسببة لهدا المرض.

Résumé

La maladie d'Alzheimer est un trouble neurodégénératif progressif caractérisé par la perte de mémoire et le déclin cognitif. Les facteurs de risque sont des caractéristiques ou des conditions qui augmentent la probabilité de développer une maladie.

Nous avons mené une enquête auprès de 29 patients et analysé les données à l'aide de SPSS pour identifier les facteurs de risque significatifs pour la maladie d'Alzheimer. Notre analyse a confirmé que l'âge et le sexe influencent significativement la prévalence de la maladie d'Alzheimer, les adultes plus âgés et les femmes étant plus touchés. L'obésité à l'âge moyen, un niveau d'éducation plus faible, des antécédents familiaux de la maladie d'Alzheimer, le tabagisme, la dépression et le stress chronique ont été identifiés comme des facteurs de risque significatifs. À l'inverse, l'engagement social semble réduire le risque de la maladie d'Alzheimer.

Cette étude a également mis en évidence l'importance de la santé bucco-dentaire, car les problèmes chroniques des gencives étaient associés à un risque plus élevé de démence. De plus, une mauvaise qualité de sommeil et l'exposition à des produits chimiques neurotoxiques, en particulier les pesticides, étaient liées à une augmentation du risque de la maladie d'Alzheimer.

De plus, le régime alimentaire et la santé intestinale étaient cruciaux, les régimes alimentaires malsains et les maladies inflammatoires de l'intestin (MII) contribuant à une prévalence plus élevée de la démence.

Dans l'ensemble, les résultats renforcent la nature multifactorielle de la maladie d'Alzheimer et la nécessité d'une approche holistique pour sa prévention et sa gestion. Les recherches futures devraient se concentrer sur ces associations pour développer des interventions ciblées.

Introduction

Introduction

Alzheimer's disease (AD) is a significant global health issue and the leading cause of dementia. It is marked by a progressive decline in cognitive function, memory loss, and behavioral changes, imposing substantial burdens on patients, their families, and society. The disease's complex pathogenesis involves the accumulation of beta-amyloid plaques, neurofibrillary tangles, widespread neuronal loss, and synaptic dysfunction (1).

Neuroinflammation, the brain's immune response to injury or infection, is an emerging research area in AD. In Alzheimer's, chronic activation of brain immune cells and infiltration of peripheral immune cells can exacerbate neuronal damage and accelerate disease progression. This underscores the intricate relationship between the immune system and neurodegeneration in AD.

Prevalence studies in Arab countries show dementia rates ranging from 1.1% to 2.3% in individuals aged 50 and older, and from 13.5% to 18.5% in those aged 80 and above. These findings highlight the substantial burden of dementia in the region and the need for further research to understand the contributing factors (2).

Focusing on Alzheimer's disease in Algeria is crucial due to its rising prevalence. By examining modifiable lifestyle factors, this research aims to offer valuable insights for developing preventive strategies and public health policies. Understanding how lifestyle factors contribute to neuroinflammation and AD progression can help design effective interventions to mitigate these risks and potentially delay the onset or progression of the disease.

This study has two main objectives:

1. Investigate the immunological hypothesis of AD: This part of the research focuses on understanding the role of neuroinflammation in Alzheimer's disease progression and how the immune system contributes to its pathogenesis.
2. Epidemiological study on risk factors: The study surveys family members of 29 AD patients in Algeria to explore how various lifestyle factors might influence the progression of Alzheimer's disease through neuroinflammation. It aims to identify lifestyle factors that lead to neuroinflammation, assess their prevalence, review relevant literature on their mechanisms, and establish correlations to better understand their role in AD development.

Literature review

I.Immunological hypothesis on Alzheimer's Disease Etiology: The Inflammatory Connection

I.1.History of the disease:

I.1.1.Alois Alzheimer's Early Contributions:

Alois Alzheimer first described the disease in 1906 after examining the brain of a deceased patient, Auguste Deter. He observed abnormal clumps (now known as amyloid plaques) and tangled bundles of fibers (now known as neurofibrillary tangles) in her brain, which became the hallmark pathological features of Alzheimer's disease (Figure 1).

Figure 1 : Auguste Deter (3).

I.1.2.Post-War revival and the path to modern understanding:

Following World War II, interest in Alzheimer's disease was renewed thanks to advances in neuropathology and the development of new staining techniques that allowed for a better visualization of its characteristics. During the 1960s and 1970s, Alzheimer's disease was recognized as a major form of dementia, not just a condition affecting the presenile population. This shift was partly due to the work of researchers like Roth and colleagues, who correlated the severity of dementia with the pathological load observed in patients, thus unifying the concepts of presenile and senile dementia.

I.1.3.The Cholinergic hypothesis and beyond:

The 1970s also witnessed the emergence of the cholinergic hypothesis of Alzheimer's, propelled by discoveries about the role of neurotransmitters in memory and cognitive function. This hypothesis suggested that Alzheimer's disease was characterized by a deficit in acetylcholine. It formed the basis for the first therapeutic strategies using cholinesterase inhibitors, although later research would show that Alzheimer's involves more complex biochemical changes beyond the cholinergic system (3) (Figure2).

Figure 2 : Alois Alzheimer (3).

I.2.Overview of Alzheimer's disease pathogenesis:

Alzheimer's disease (AD) is a progressive neurodegenerative condition characterized by significant loss of neurons, particularly in the hippocampus and cerebral cortex. it is characterized by the presence of extracellular amyloid plaques and intracellular neurofibrillary tangles (NFTs), surrounded by immune cells, particularly microglia (4). Clinically, AD manifests as progressive cognitive decline (5). Amyloid beta (Aβ) is the main component of amyloid plaques, generated from improper cleavage of amyloid precursor protein (APP), while hyperphosphorylated tau protein forms NFTs. The accumulation of Aβ and deposition of NFTs are central to AD pathology, although the mechanisms underlying their accumulation are not fully understood (4).

Aβ aggregation initiates in the preclinical phase of AD, often occurring years before clinical symptoms emerge. Subsequently, tau pathology typically follows Aβ plaque deposition (6,7),(8). Aβ acts as a damage-associated molecular pattern (DAMP), binding to receptors such as toll-like receptors (TLRs) (9), receptor for advanced glycation end products (RAGE), and nucleotide-binding oligomerization domain-like receptors (NLRs). This binding activates microglia, leading to the release of cytokines, chemokines, and recruitment of more glial cells to the Aβ site (Figure 3).

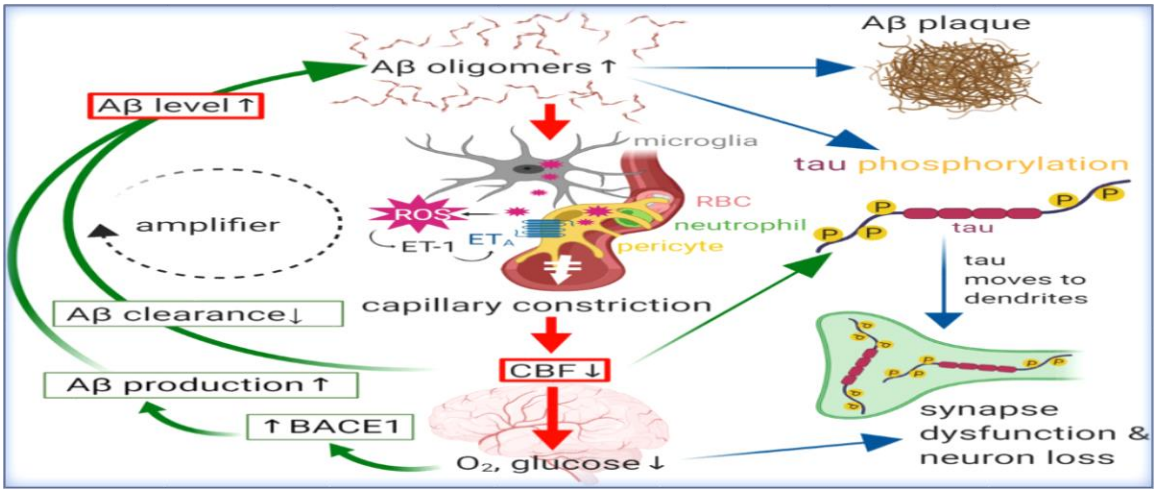

Figure 3 : Amyloid beta and Tau cascade in Alzheimer's disease (10).

Activated microglia and astrocytes attempt to clear Aβ through phagocytosis (11,12), but when clearance mechanisms fail, chronic inflammation ensues, accompanied by the release of proinflammatory and toxic molecules like cytokines, reactive oxygen species (ROS), and nitric oxide (NO) (13), exacerbating neurotoxicity. Various CNS cells, including neurons, oligodendrocytes, vascular endothelial cells, and pericytes, also contribute to the inflammatory microenvironment (14).

The longstanding amyloid-beta hypothesis has proven insufficient for fully explaining Alzheimer's disease (AD), prompting researchers to explore other mechanisms, particularly involving the immune system and inflammatory processes. This research focuses on how chronic inflammation and immune system anomalies may drive AD progression. The concept of inflammaging, or chronic inflammation linked to aging, is examined for its role in AD pathogenesis. Additionally, connections between AD and chronic inflammatory diseases highlight the significant impact of immunological factors. This section will explore these hypotheses, illustrating how immune responses and systemic inflammation may be crucial in the neurodegenerative pathways of AD.

I.2.2.Anatomy of Alzheimer's Disease:

Hippocampus

The hippocampus is a critical region for memory formation and spatial navigation. It is one of the first areas to show signs of atrophy in Alzheimer's disease. This early damage to the hippocampus leads to the initial symptoms of memory impairment commonly observed in patients (15).

Cerebral Cortex

The cerebral cortex, responsible for higher cognitive functions such as reasoning, language, and executive functions, undergoes significant atrophy as Alzheimer's disease progresses. The temporal lobes are affected first, followed by the parietal and frontal lobes. This cortical thinning contributes to the decline in cognitive abilities (16).

Entorhinal Cortex

The entorhinal cortex acts as a hub within a network involved in memory and navigation. It is one of the earliest sites of neurodegeneration in Alzheimer's disease, experiencing considerable neuronal loss. This disruption affects the communication between the hippocampus and other cortical areas, exacerbating memory deficits (15).

Neuronal and Synaptic Loss

Neuronal loss is particularly severe in the entorhinal cortex and hippocampus, resulting in disrupted connectivity and impaired synaptic plasticity. Additionally, synaptic loss is a critical feature, as reduced synaptic density correlates with the severity of cognitive decline and the clinical manifestations of Alzheimer's disease (17)(18).

Amyloid Plaques

Amyloid plaques, composed of aggregated amyloid-beta (Aβ) peptides, accumulate extracellularly in the brain parenchyma and blood vessels. These plaques are neurotoxic and

disrupt cell-to-cell communication, contributing to the neurodegenerative process in Alzheimer's disease (19).

Neurofibrillary Tangles

Neurofibrillary tangles, formed from hyperphosphorylated tau protein, accumulate within neurons. This intracellular accumulation leads to microtubule destabilization, impaired neuronal transport, and eventually, neuronal death. The presence of these tangles is a hallmark of Alzheimer's disease pathology (20).

Cerebral Atrophy and Ventricular Enlargement

Advanced Alzheimer's disease is characterized by widespread cerebral atrophy, observable through neuroimaging techniques such as MRI. The significant loss of brain tissue results in the enlargement of the ventricles, which are fluid-filled spaces in the brain. This ventricular enlargement serves as a biomarker for disease progression (21)(22).

Vascular Changes and Blood-Brain Barrier Dysfunction

Vascular changes play a crucial role in Alzheimer's disease pathology. Cerebral amyloid angiopathy (CAA) involves the deposition of Aβ in cerebral blood vessel walls, contributing to vascular dysfunction and disrupted cerebral blood flow. Additionally, blood-brain barrier (BBB) dysfunction is common, leading to increased permeability and the infiltration of peripheral immune cells, which exacerbates neuroinflammation (23) (Figure 4).

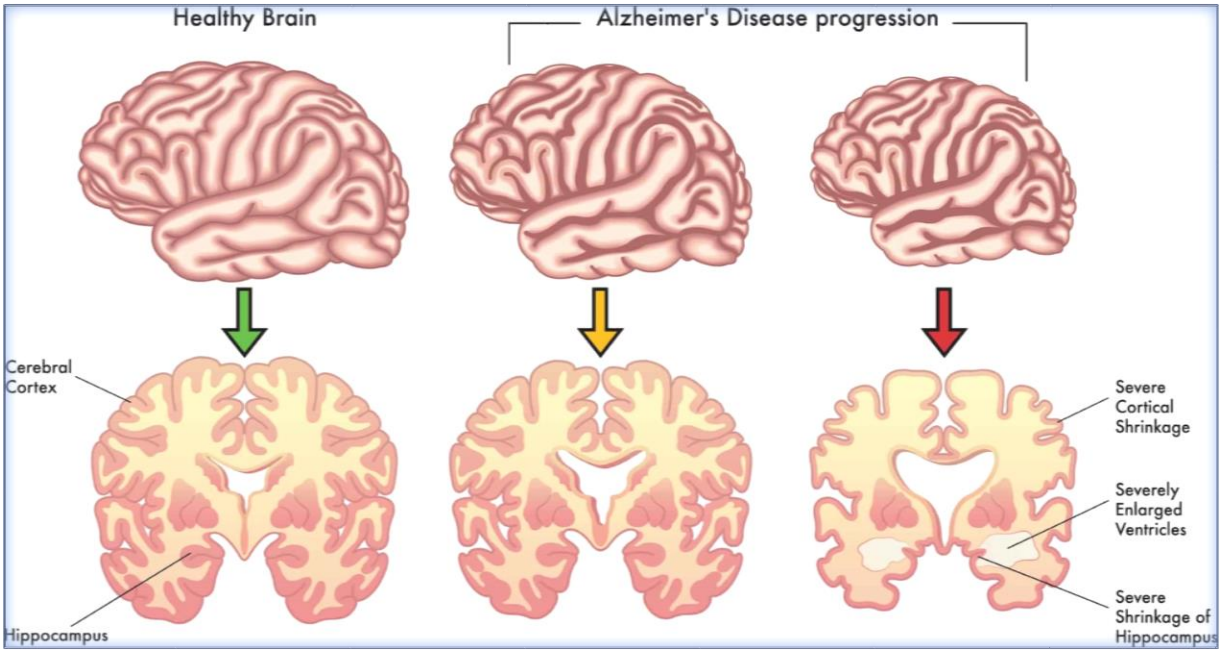

Figure 4 : healthy brain and AD patients brain (24).

I.3.The role of Amyloid-Beta (Aβ) as an immunological player in Alzheimer's disease:

Amyloid beta has a variety of roles and impacts on the immune system within and outside of alzheimer's disease (Figure 5).

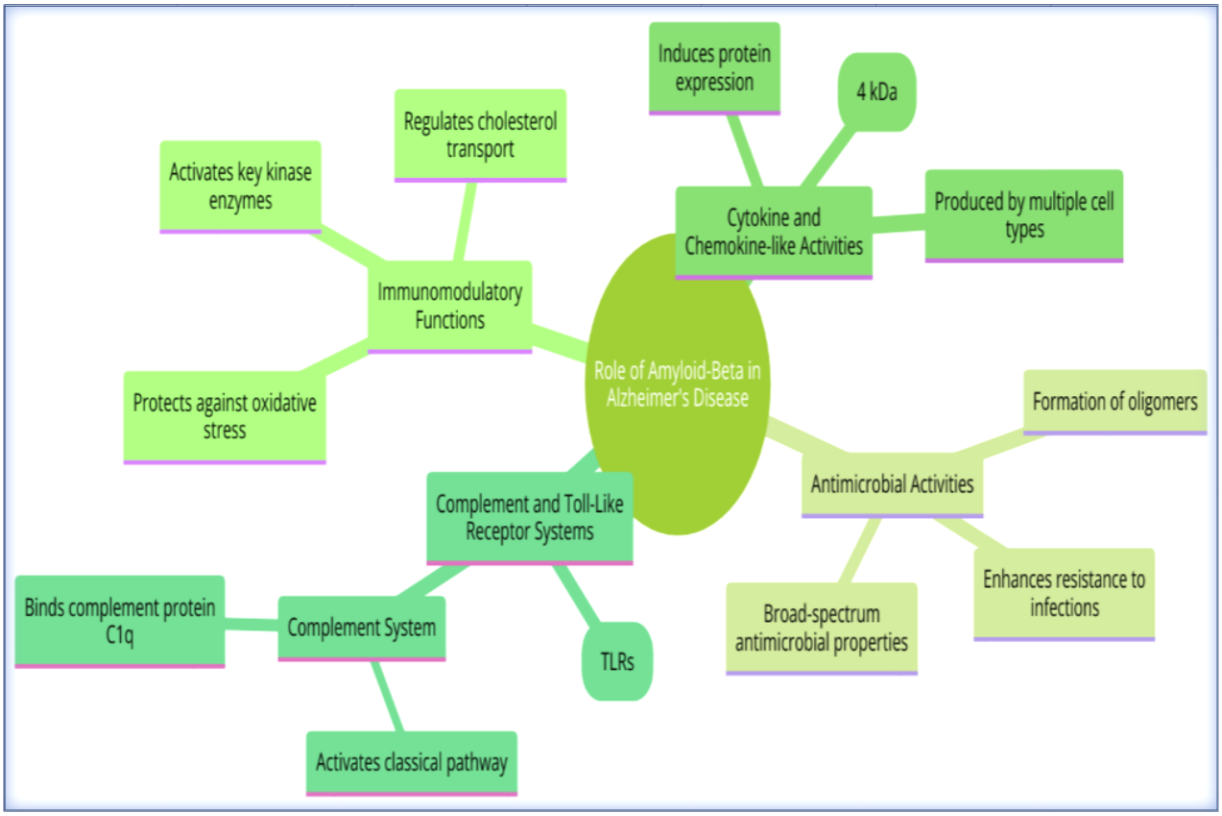

Figure 5 : Summary of Amyloid-Beta's role in Alzheimer's disease.

I.3.1.Amyloid-Beta as an immunomodulatory molecule:

Despite decades of study, Aβ remains a complex and not fully understood molecule in the context of AD. Its presence, whether as a consequence or cause, is central to AD pathology. The existence of specific enzymatic pathways for Aβ biosynthesis, along with selective routes for its uptake, breakdown, and clearance, suggests that Aβ has normal physiological roles beyond being a mere toxic entity. Proposed functions for Aβ include regulating cholesterol transport, protecting against oxidative stress, and activating key kinase enzymes, though these do not fully encapsulate its role in AD (25). Considering Aβ as an innate immunopeptide (antimicrobial peptide/cytokine/chemokine) aligns with its multifaceted role in AD.

I..3.2.Antimicrobial and immunomodulatory functions of Amyloid-Beta:

Aβ functions as an AMP (Antimicrobial peptides) (26). Various studies have shown that Aβ possesses broad-spectrum antimicrobial properties against viruses, bacteria, and fungi, facilitated by the formation of oligomers that disrupt membranes and trap pathogens. Overexpression of Aβ enhances resistance to infections by both bacteria and viruses (27). Like AMPs, Aβ's actions are influenced by cholesterol, Zn^{2+}, and Cu^{2+}. As an immunopeptide, Aβ modulates innate immune responses and binds to GAGs via its H13HQK16 (BBXB) motif (28).

I.1.3.3Cytokine and Chemokine-like activities of Amyloid-Beta:

Aβ meets the functional definition of a cytokine. It is a small protein (4 kDa) that acts as an immunomodulatory signaling molecule, mediating intercellular interactions and regulating immunity and inflammation. Through c-Jun N-terminal kinase (JNK-AP1) pathways.

Aβ induces the expression of monocyte chemoattractant protein-1 (MCP-1), growth-related oncogene (GRO), IL-1β, and IL-6 (29).

Aβ also affects gene expression pathways crucial for vesicle trafficking, cell adhesion, actin cytoskeleton dynamics, insulin signaling, and synaptophysin downregulation (30). Aβ can be produced by neurons, astrocytes, neuroblastoma cells, hepatoma cells, and fibroblasts. Its interactions with other cytokines display pleiotropism, redundancy, and synergism.

While Aβ lacks the defining cysteine disulfide loops of chemokines, it fits functionally within the AMP-chemokine spectrum.

I.3.4.Amyloid-Beta's role in the complement and Toll-Like receptor systems:

Similar to other cytokines, Aβ interacts with and is influenced by the TLR and complement systems. In the early stages of AD, fibrillar Aβ engages TLR2 and TLR4, promoting microglial phagocytosis of Aβ (31); TLR7, TLR8, and TLR9 enhance microglial Aβ uptake at later stages (32). Aβ also binds to the complement protein C1q, activating the classical pathway and causing complement-mediated neuronal toxicity. Complement proteins are integral to Aβ plaques, accumulating early in Aβ deposition (33,34) (Figure 6).

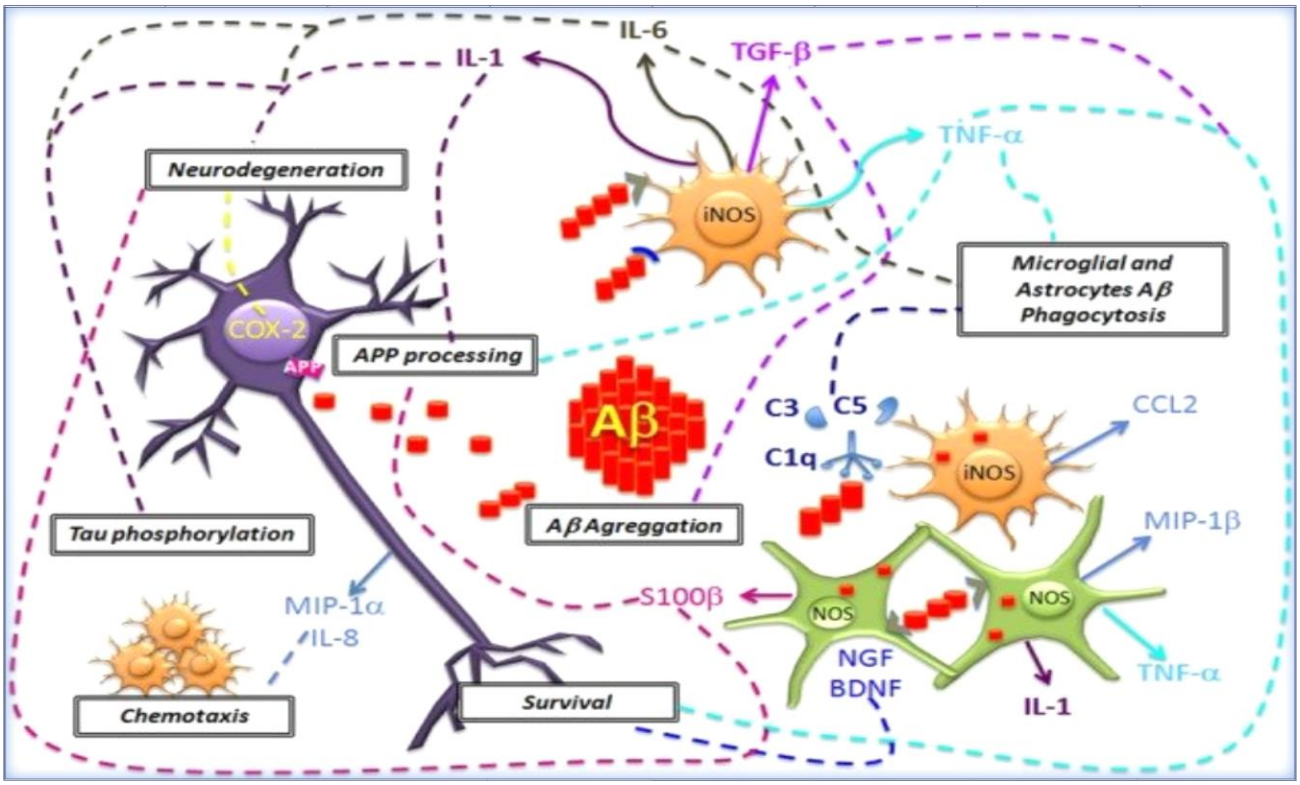

Figure 6 : Different interaction of Amyloid beta in AD (35).

I.4.The Role of Tau as an immunological player in Alzheimer's disease:

I.4.1.Mechanisms of Tau pathology:

-Hyperphosphorylation of Tau: Hyperphosphorylation of tau is a hallmark of AD and is mediated by kinases such as glycogen synthase kinase-3β (GSK-3β), cyclin-dependent kinase 5 (CDK5), and microtubule affinity-regulating kinase (MARK). This modification reduces tau's affinity for microtubules, causing it to aggregate into paired helical filaments (PHFs) and eventually NFTs, which are toxic to neurons (36,37).

-Aggregation into NFTs: The formation of NFTs involves the assembly of hyperphosphorylated tau into insoluble aggregates. These NFTs accumulate within neurons, leading to cellular dysfunction and apoptosis. The spread of tau pathology follows a characteristic pattern, beginning in the entorhinal cortex and progressing to the hippocampus and neocortex, correlating with cognitive decline in AD (36,37) (Figure 7).

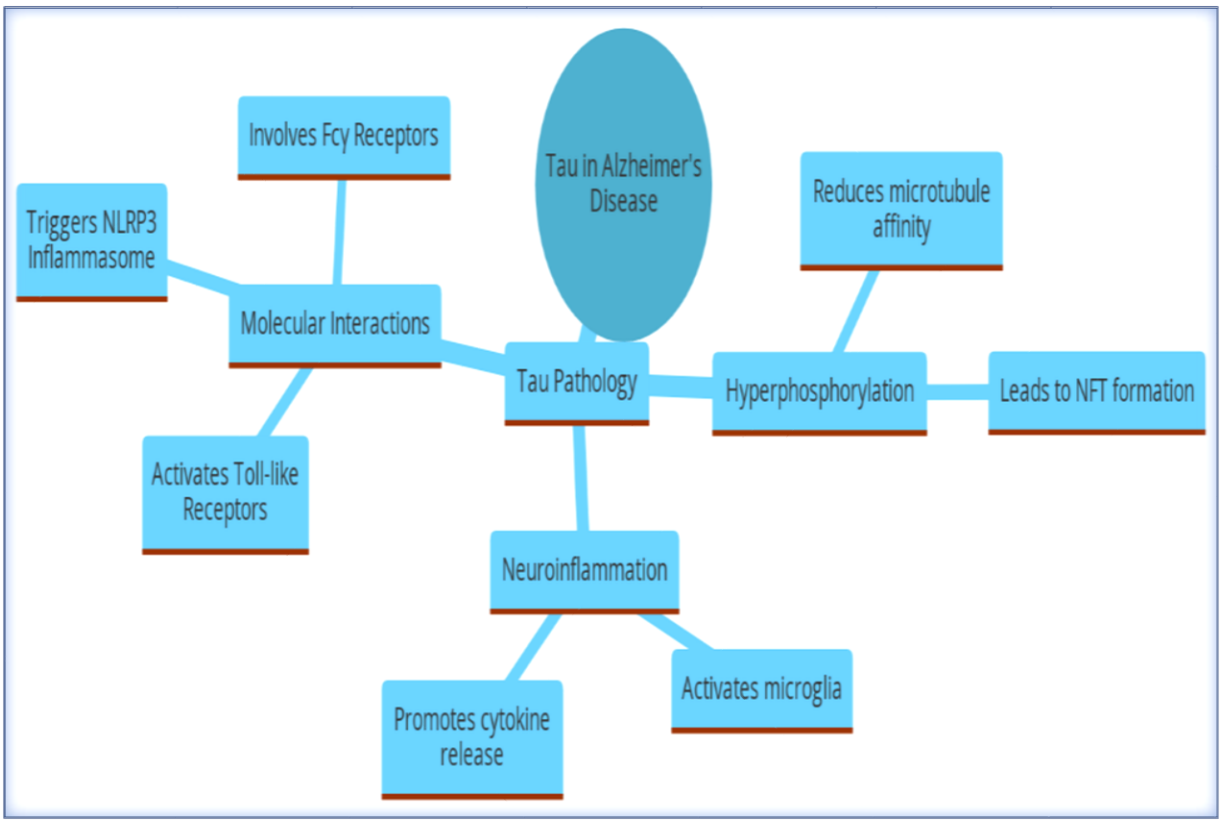

Figure 7 : summary of Tau pathology in Alzheimer's disease

I.4.2.Interplay Between Tau pathology and neuroinflammation:

-Microglial activation**:** Microglia, the primary immune cells of the CNS, play a crucial role in responding to pathological changes. Aβ plaques activate microglia, which release pro-inflammatory cytokines such as IL-1β, IL-6, and TNF-α. These cytokines can induce tau hyperphosphorylation, exacerbating tau pathology (36,37).

-Cytokine signaling: Pro-inflammatory cytokines from activated microglia and astrocytes further promote tau pathology. For instance, IL-1β can activate p38 MAPK, which increases tau phosphorylation. Similarly, TNF-α induces GSK-3β expression, leading to enhanced tau hyperphosphorylation (36,37).

-Astrocytes and Tau pathology: Reactive astrocytes contribute to neuroinflammation by releasing pro-inflammatory cytokines and ROS, damaging neurons and exacerbating tau pathology. Astrocytes can also propagate tau pathology by releasing tau-containing extracellular vesicles, which can be taken up by neighboring neurons (36,37).

1.4.3.Molecular interactions of Tau and immune system components:

-Toll-like receptors (TLRs): TLRs are pattern recognition receptors that detect DAMPs. Hyperphosphorylated tau can activate TLR4, leading to the release of pro-inflammatory cytokines and further promoting neuroinflammation. This interaction highlights tau's role as a DAMP in AD (38,39).

-NLRP3 inflammasome: The NLRP3 inflammasome is a critical component of the innate immune system. Tau aggregates can activate the NLRP3 inflammasome in microglia, resulting in the release of IL-1β and perpetuating neuroinflammation. This creates a feedback loop where neuroinflammation and tau pathology exacerbate each other (38,39).

-Fcγ receptors:Fcγ receptors on microglia mediate the clearance of tau aggregates through phagocytosis. However, this process can also trigger inflammatory pathways, contributing to chronic inflammation in the brain. FcγRIIb has been shown to mediate tau-induced neurotoxicity and memory impairment in AD, linking immune receptor activation to tau pathology (40) (Figure 8).

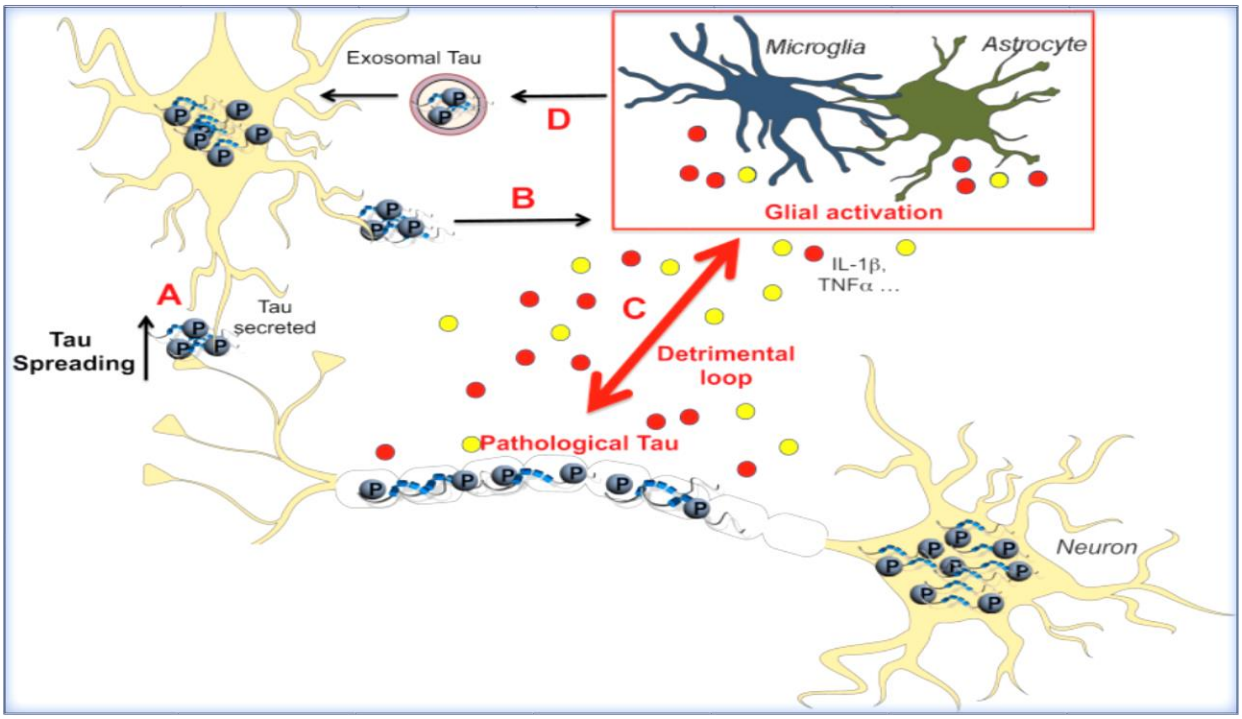

Figure 8 : innate immune response and Tau pathology (39).

I.5.The role of neuroinflammation in Alzheimer's Disease: Principal agents and biomarkers:

Neuroinflammation is emerging as a significant factor in Alzheimer's disease (AD), interwoven deeply with the progression and symptomatology of this neurodegenerative condition. As we delve into the biochemical cascades and cellular activities central to AD, it becomes evident that inflammatory processes are not merely bystanders but active participants in the disease's pathogenesis

Amyloid precursor protein (APP) is a substantial glycosylated membrane protein processed through two proteolytic pathways involving secretases: initially alpha then gamma or beta then gamma. This results in the formation of 40–42 amino acid long amyloid-beta (Ab) peptides, predominantly Ab40, with a lesser proportion being the more amyloidogenic Ab42, which tends to aggregate into fibrils and accumulate over time. In individuals with Down syndrome, APP processing is often disrupted in astrocytes and neurons, leading to intracellular build-up of the Ab42 fragment, possibly related to mitochondrial dysfunctions (41,42) (Figure 9).

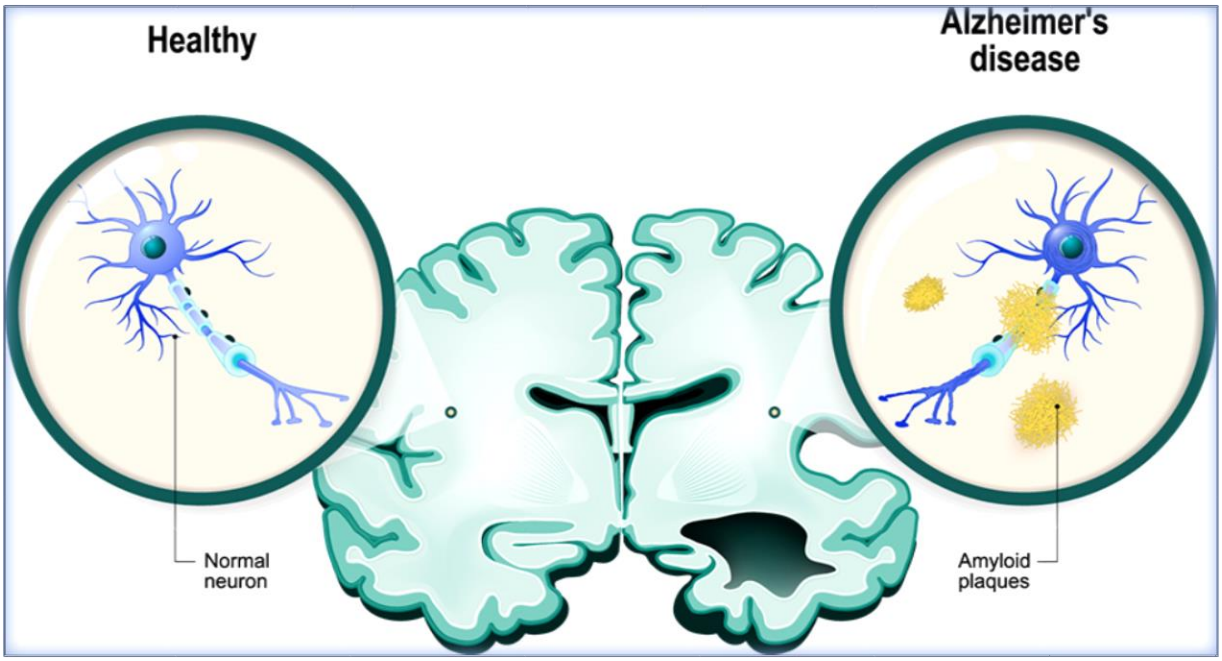

Figure 9 : Amyoild Beta plaques (43).

Activated microglia and astrocytes may enhance Ab deposition; studies in mouse models indicate that inflammatory conditions can increase amyloid deposition (44). Cytokines can further upregulate the mRNA, protein, and enzymatic activity of beta-secretase (BACE1) (45), a key enzyme in neuronal Ab production (46), whose transcription is also stimulated by TNF-alpha-activated nuclear factor kappa B (NF-kB) signaling, resulting in increased Ab production (47). The literature describes a variety of pro-inflammatory and anti-inflammatory cytokines, where pro-inflammatory cytokines are important for promoting inflammatory responses that can damage tissues, while anti-inflammatory cytokines regulate these responses (Figure 10).

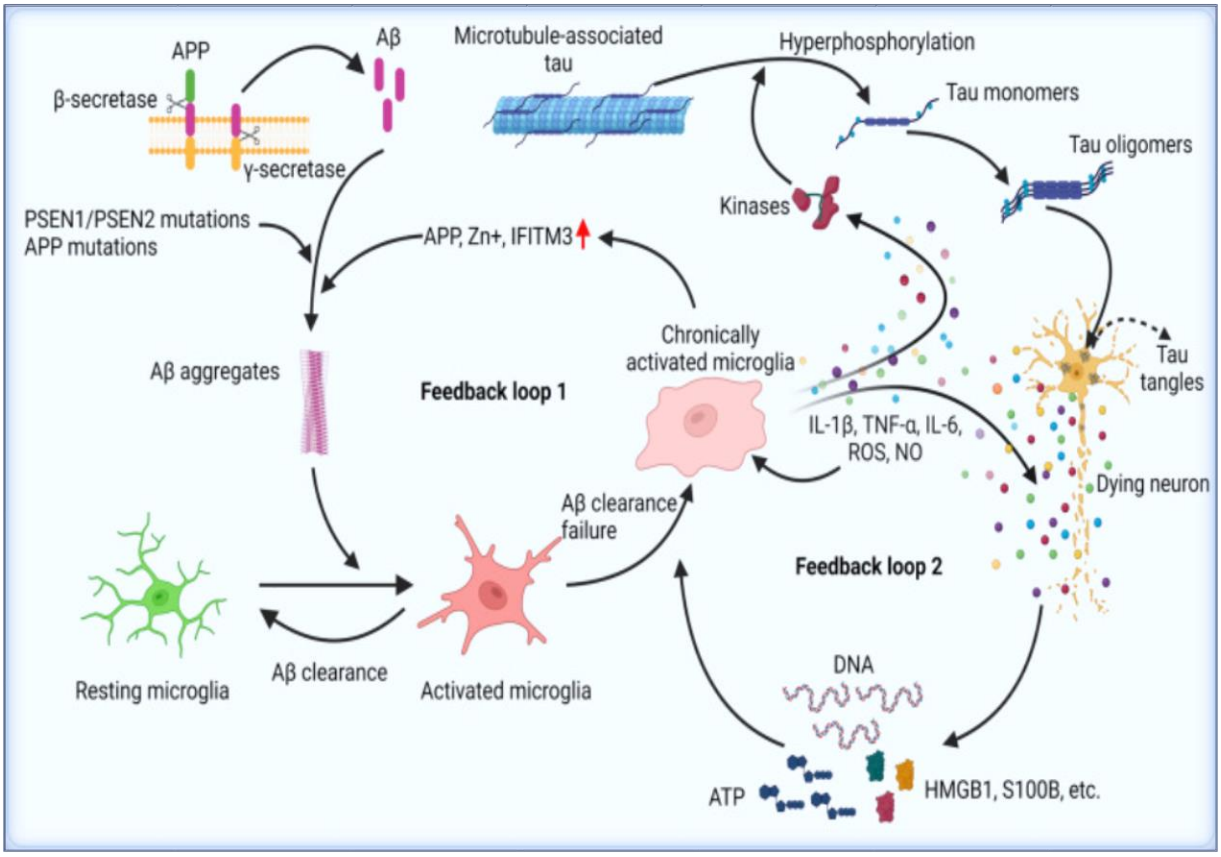

Figure 10 : Neuroinflammation in AD (48).

Cerebrospinal fluid (CSF) analysis in AD, which routinely measures Ab and tau levels as indicators of AD pathology, has shown inhomogeneous results regarding cytokine levels in AD subjects compared to controls, with some studies noting comparable levels while others found increased concentrations of cytokines such as TNF-alpha, IL-6, IL-8, and GM-CSF in AD subjects (49). Recent evaluations of various inflammatory markers in the CNS have underscored the complex interplay of inflammatory processes in AD pathology (50), highlighting the need for further detailed investigations into these mechanisms.

I.6.Role of immune cells:

I.6.1.Microglial cells:

Microglia, the primary immune cells of the central nervous system (CNS), are integral to the brain's response to injury and disease. It has been proposed that the activation of microglia and the subsequent release of pro-inflammatory mediators are crucial contributors to neuronal damage (41). Upon encountering an acute inflammatory insult in the brain, microglia mount an initial defensive response aimed at tissue repair. However, if the inflammatory stimulus persists, this response can become chronic and detrimental, exacerbating neuronal dysfunction, injury, and loss (51).

-Microglia activation:Postmortem analyses of Alzheimer's disease (AD) patients' brains consistently reveal the presence of reactive microglia colocalized with amyloid plaques (52). various amyloid peptides, fibrils, and amyloid precursor protein (APP) have been identified as potent activators of glial cells, instigating an inflammatory response and promoting the release of neurotoxic cytokines from microglia (53). Amyloid-beta (Aβ) specifically can stimulate the NF-kB-dependent pathway and, upon binding to microglial cell surfaces, activate extracellular signal-regulated kinase (ERK) and mitogen-activated protein kinase (MAPK) pathways. This cascade triggers the expression of pro-inflammatory genes (54,55). Both soluble and fibrillary forms of Aβ appear to induce NADPH oxidase-mediated priming in microglial cells, resulting in the release of reactive oxygen species (ROS) that contribute to neurotoxicity (56) (Figure 11).

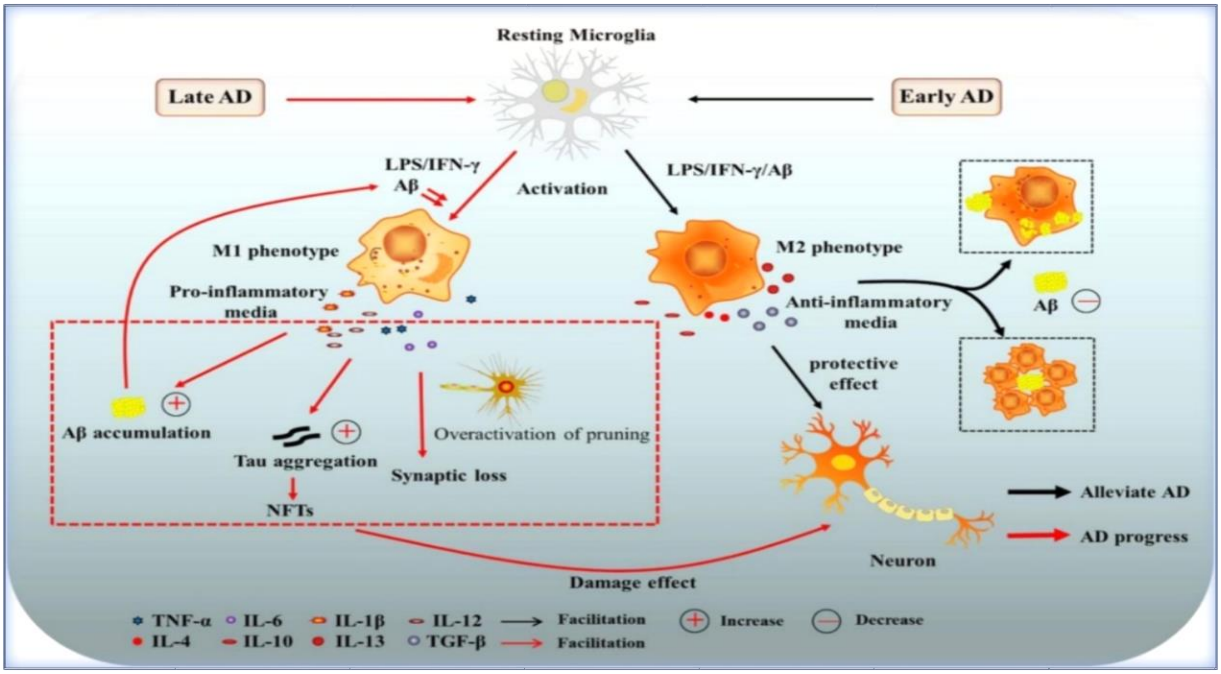

Figure 11 : The role of Microglial cells in AD Neuroinflammation (57).

I.1.6.2.Astrocytes:

Astrocytes, a type of microglial cell, play numerous vital roles within the CNS. They are actively involved in synaptogenesis, neurogenesis, neurotransmission, and the formation and maintenance of the blood-brain barrier (BBB). Additionally, they are crucial for metabolic regulation, ion balance, and synaptic transmission. Pathological astrocytes have been identified in a variety of neurological disorders, including AD, amyotrophic lateral sclerosis (ALS), multiple sclerosis (MS), PD, and epilepsy.

-Astrogliosis: characterized by the proliferation and hypertrophy of astrocytes, has been observed in postmortem brain tissues from AD patients. A correlation exists between the degree of astrogliosis and the severity of cognitive impairment, although astrogliosis can also be found in regions devoid of Aβ pathology.

Astrocytes express receptors for various chemokines and inflammatory cytokines, such as interleukin-1 beta (IL-1β) and tumor necrosis factor-alpha (TNFα) (58), which can activate these glial cells. The C-terminal 100 amino acids of beta-amyloid precursor protein (βAPP), located in senile plaques, can induce astrogliosis and subsequent neuronal death (46). While microglia are primarily responsible for the phagocytosis and degradation of Aβ (59), astrocytes also play a significant role in the clearance and degradation of this peptide (Figure 12).

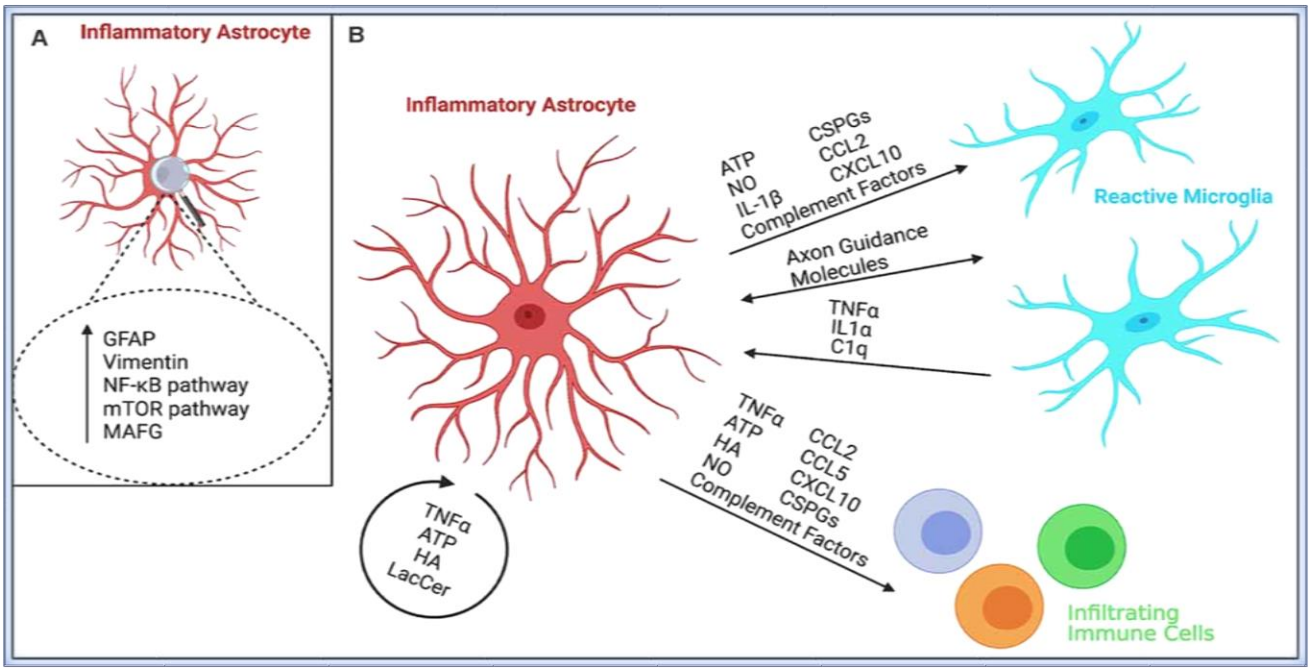

Figure 12 : The role of Astrocytes in Neuroinflammation (60).

I.7.The role of autoimmunity in Alzheimer's Disease (AD):

I.7.1.Potential autoimmune mechanisms in AD:

Autoimmunity in Alzheimer's disease (AD) suggests that the disease may be driven, at least in part, by autoimmune reactions where host antibodies target self-proteins (autoantibodies) in the brain. This hypothesis has significant implications for understanding AD pathogenesis and developing new treatment strategies (61,62). Typically, immune tolerance prevents the immune system from attacking the body's own cells. However, in AD, this tolerance is disrupted, leading to autoimmunity (61,62).

-Disruption of immune tolerance: Immune surveillance of brain antigens that drain into the meningeal lymphatic system may expose brain macromolecules to the peripheral immune system (63). The discovery of meningeal lymphatic vessels by Louveau et al. (64) revealed a connection between the central nervous system (CNS) and the peripheral immune system, challenging the traditional notion of the brain's immune privilege (65,66). These vessels drain cerebrospinal fluid (CSF) and neuronal antigens, subjecting them to immune surveillance by circulating lymphocytes (67,68). Impaired meningeal lymphatic function has been implicated in AD pathology and other autoimmune neurodegenerative diseases such as multiple sclerosis and autoimmune encephalomyelitis (69,70).

Uncovering the autoimmune components of AD is crucial for developing new concepts for pathogenesis, diagnosis, and therapy.

I.8.The Role of the Gut-Brain Axis in Alzheimer's Disease pathogenesis: An immunological Perspective:

I.8.1.Neuroinflammation and the Gut-Brain Axis in Alzheimer's Disease:

The GMB, consisting of trillions of bacteria, archaea, protozoa, viruses, and fungi, has been shown to regulate neuroinflammation in neurological conditions, including multiple sclerosis (71), Parkinson's disease (72), and AD (73).

GMB-mediated regulation of neuroinflammation may occur through direct or indirect mechanisms. Changes in the GMB can alter microbial-derived metabolites and peripheral immunity, potentially affecting the central nervous system (CNS) immune response (74). Studies indicate that AD patients have an altered GMB compared to those without AD (75). Additionally, manipulating the GMB in AD mouse models can alter pathology and neuroinflammation (76,77). The precise mechanisms by which the GMB influences AD remain to be elucidated, but studies in both human patients and mouse models of Aβ amyloidosis implicate the GMB in AD pathogenesis. Understanding these mechanisms may lead to microbiome-mediated therapeutic strategies for AD.

I.8.2.Human evidence of GMB alterations in Alzheimer's Disease:

Initial studies in 2017 showed that amyloid-positive individuals/AD patients have an altered GMB composition compared to individuals without amyloid/AD. Cattaneo et al. measured plasma levels of RNAs encoding selected cytokines and stool abundance of particular GMB taxa in 83 individuals, revealing an increase in mRNA encoding pro-inflammatory cytokines IL6, CXCL2, NLRP3, and IL1β, and a decrease in IL-10 in amyloid-positive patients compared to amyloid-negative individuals (78).

Apositive correlation was found between pro-inflammatory cytokines and Escherichia/Shigella, and a negative correlation with Eubacterium rectale. Vogt et al. conducted 16s ribosomal RNA amplicon sequencing on DNA from fecal matter of 50 participants, showing decreased GMB bacterial diversity in AD patients, with reductions in Firmicutes and Bifidobacterium and increases in Bacteroidetes (75).

I.8.3The Vagus nerve: A conduit for Gut-Brain communication:

The vagus nerve provides a direct connection between the gut and the brain, allowing bidirectional communication and mediating gut-brain interactions. Microbiota-derived molecules, such as neurotransmitters and hormones, can affect vagus nerve firing and influence brain function (79). Gut-derived neurotransmitters play roles in mood regulation and psychiatric disorders, while SCFAs and gut-derived hormones interact with vagal fibers

(79,80). Vagus nerve stimulation has been shown to decrease neuroinflammation and induce anti-inflammatory microglial phenotypes in AD models, suggesting a potential role for gut-derived signaling in AD progression. Further research is needed to explore the involvement of vagus nerve signaling in the GMB-AD relationship (Figure 13).

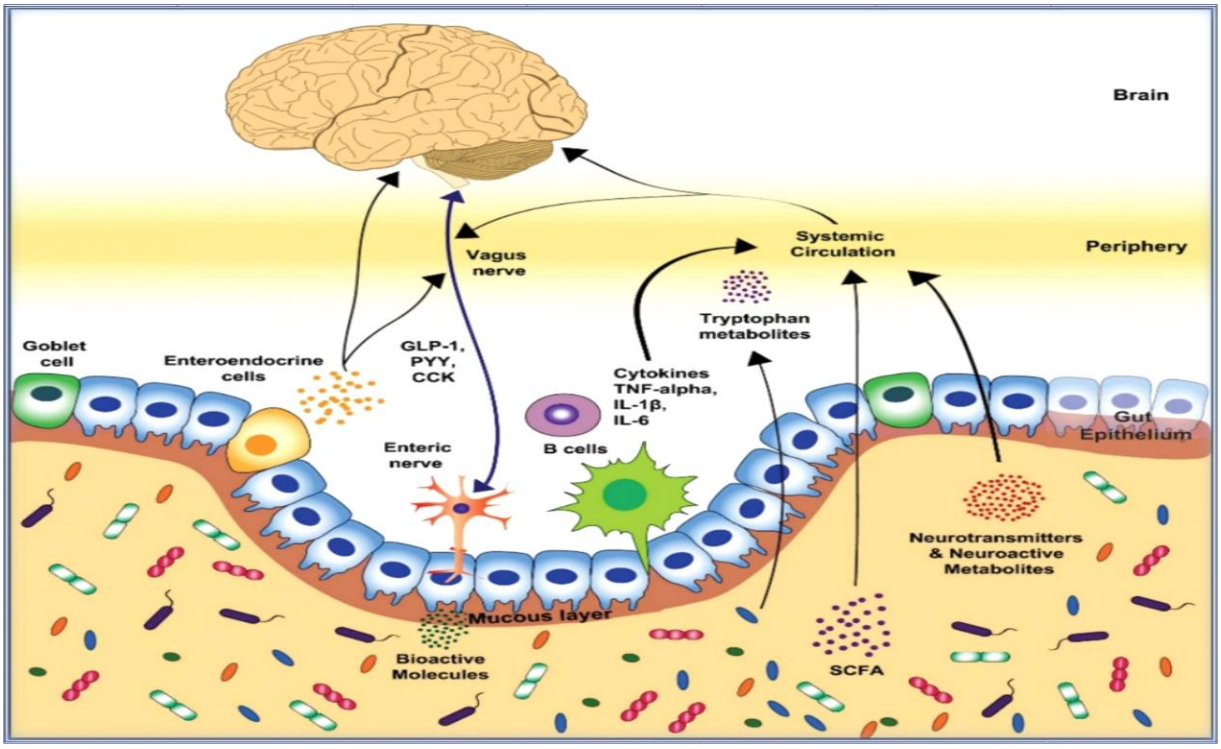

Figure 13 : The key routes of communication in gut-brain axis (81).

II:Risk factors for Alzheimer's Disease and their immunological impact

II.1.Demographic factors :

II.1.1. Inflammation related to age in Alzheimer’s disease:

The aging process diminishes the efficacy of immune cells in clearing senescent cells, partly due to involutional changes within the immune system. As a result, the number and lifespan of SASP-secreting cells increase, leading to tissue and overall bodily aging and heightening the risk of age-related diseases, including AD (82).

-Aging process: During aging, three distinct types of changes are observed

- Primary changes: involve genomic disturbances, such as increased mutation rates, telomere shortening (Hayflick limit), and epigenetic modifications like DNA methylation and acetylation, which disrupt protein homeostasis in cells.

-Secondary changes: which stem from primary alterations, include mitochondrial dysfunction and cellular senescence (83).

-The third type: integrative changes, encompasses the depletion of stem cell pools and disruptions in intercellular communications (84). Aging is commonly categorized into three types: natural or physiological, premature or pathological, and delayed (85).

-Cellsenescence: Cellular aging is marked by cells' inability to progress beyond the G1 or G2/M phases of the cell cycle. This stagnation is characterized by abrupt changes in cell size and shape, cytoplasmic vacuolization, alterations in nuclear and chromatin organization, and resistance to apoptosis signals (86). Nevertheless, these cells remain metabolically active and secrete a distinctive pro-inflammatory cocktail known as the senescence-associated secretory phenotype (SASP).

-SASPs: They comprise a variety of components, including pro-inflammatory cytokines (IL-1α, IL-1β, IL-6, IL-8, TNFα), chemokines (CCL2, CCL5, CCL20), growth factors (TGF, EGF, bFGF, HGF, VEGF), metalloproteinases (MMP-1, -3, -10, -12, -13, -14), extracellular matrix components (fibronectin, collagen, laminin), aging-associated beta-galactosidase (SA-β-Gal), and more (Figure 14).

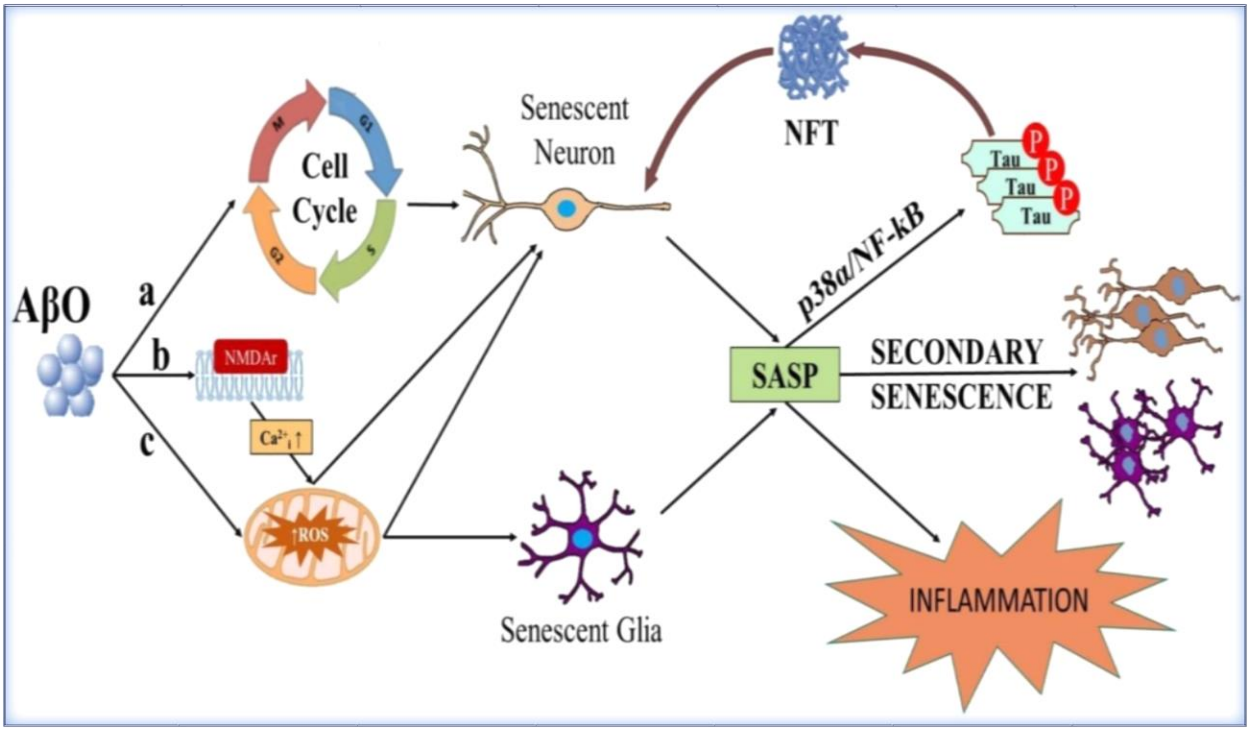

Figure 14 : Cellular Senescence and AD (87).

II.1.2.Sex as a risk factor for Alzheimer's disease:

-Estrogen hypothesis of AD development:

The female sex is a significant risk factor for late-onset Alzheimer's disease (LOAD) (88), and women generally exhibit a higher susceptibility to aging-related neurodegenerative diseases compared to men (89).

-Estrogen: This increased risk is likely associated with the "estrogen hypothesis." Estrogen and estradiol play crucial roles in the brain by regulating glucose metabolism, glycolysis, oxidative phosphorylation, and ATP generation in neurons. They also enhance mitochondrial bioenergetics and calcium homeostasis, reduce reactive oxygen species (ROS) production, and protect cells from apoptosis. Additionally, estrogen exerts anti-inflammatory effects, particularly on microglial cells (90). During peri- and post-menopause, the decline in estrogen levels leads to disruptions in these processes, which are otherwise maintained by higher hormone concentrations. This dysregulation of brain glucose metabolism and the resulting accumulation of damage-associated molecular patterns (DAMPs), combined with immune system activation, including microglia, eventually provoke chronic low-grade inflammation and elevate its levels (90).

II.2.Lifestyle factors :

II.2.1.Obesity and Alzheimer's Disease

Obesity is a chronic condition marked by an excessive accumulation of adipose tissue and various metabolic disorders. This condition is linked to elevated levels of several proinflammatory markers, such as C-reactive protein (CRP) (91), plasminogen activator inhibitor-1 (PAI-1) (92), interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α) (93), monocyte chemoattractant protein-1 (MCP-1 or CCL2) [117], and serum amyloid A (SAA) (94). Additionally, obesity is frequently associated with cardiovascular diseases and type 2 diabetes mellitus (T2DM) (95), which are also risk factors for Alzheimer's disease (AD).

Obesity contributes to the risk of AD through various mechanisms, including chronic inflammation, insulin resistance, and disrupted lipid metabolism. Understanding these connections is essential for developing targeted interventions to mitigate AD risk in obese individuals.

II.2.2.Smoking and Alzheimer's Disease:

-Association between smoking and AD risk:

Smoking has been widely studied as a potential risk factor for Alzheimer's disease (AD). Epidemiological evidence suggests that smoking significantly increases the risk of developing AD and other forms of dementia. Research indicates that smokers have a 1.7-fold higher risk of developing AD compared to non-smokers. This increased risk is particularly pronounced in individuals carrying the apolipoprotein E (APOE) ε4 allele, which is the strongest genetic risk factor for late-onset AD. The interaction between smoking and the APOE ε4 allele exacerbates the risk, leading to an even higher probability of AD development (96).

II.2.3.Alcohol consumption and Alzheimer's Disease:

¶

-Association between alcohol consumption and AD Risk:

Alcohol consumption is a modifiable behavior that has emerged as a potential factor influencing dementia risk. Recent studies have investigated the relationship between alcohol intake and the risk of developing Alzheimer’s disease (AD), vascular dementia (VaD), and all-cause dementia (ACD). Several systematic reviews and meta-analyses have concluded that light-to-moderate alcohol consumption is associated with a reduced risk of these forms of dementia compared to abstainers. Specifically, light-to-moderate drinking, defined as up to 4 drinks per week or 6 grams per day, has been linked to a 25–38% reduction in dementia risk. However, the protective effects are predominantly observed with wine consumption.

On the other hand, excessive alcohol consumption, defined as 23 drinks per week or 12.5 grams per day, significantly increases the risk of AD and other neurodegenerative conditions. Observational studies may underestimate the detrimental effects of long-term heavy drinking due to biases such as the exclusion of individuals with alcohol-related dementia (ARD) . Furthermore, heavy drinkers with early cognitive impairment are often screened out of studies, leading to potential underestimation of the true impact of excessive alcohol consumption on dementia risk.

Overall, while light-to-moderate alcohol consumption may offer some protective effects against AD, heavy drinking is a significant risk factor for neurodegeneration. The complexity of alcohol's impact on AD underscores the importance of personalized and context-specific recommendations for alcohol consumption (97).

II.2.4.Loneliness, social life, and Alzheimer's Disease:

-Biological mechanisms of loneliness-induced neurodegeneration:

Loneliness is linked to several biological mechanisms that may contribute to neurodegeneration. For instance, higher anxiety levels in individuals with AD have been associated with increased functioning of strychnine-sensitive glycine receptors and a selective reduction in NMDA receptor NR2A density. In terms of brain structure, anxiety in AD has been correlated with atrophy in the right precuneus and inferior parietal lobule, as well as hyperperfusion of the bilateral anterior cingulate cortex (98).

Moreover, studies have shown that loneliness is associated with the hallmarks of AD, including amyloid burden and tauopathy, particularly in older adults with normal cognition. These associations were found to be stronger among APOE ε4 carriers. Despite these findings, the association between persistent loneliness and AD risk was notably significant in APOE ε4 noncarriers, suggesting that loneliness could be an independent risk factor for AD, with unique mechanisms affecting cognitive functioning.

II.2.5.Sleep and Alzheimer's Disease:

-Association between sleep disturbance and AD risk:

Various animal models of AD and sleep disturbances have been used to assess the causal relationship between sleep disturbance and AD and the molecular or cellular mechanisms potentially underlying this link. Kang et al. (2009) were the first to report that chronic sleep

restriction accelerates Aβ deposition in the brain using two transgenic AD mouse models (APPswe and APPswe/PS1dE9 mice). Other studies have also demonstrated that sleep deprivation or restriction in various AD models exacerbates AD-related biochemical or pathological changes in mice brains, such as an increase in Aβ or phosphorylated tau , an increase in insoluble phosphorylated tau and glial fibrillary acidic protein levels , and an increase in Aβ40, Aβ42, and β-site amyloid-precursor-protein-cleaving enzyme 1 (BACE1), which produce toxic Aβ species (99).

II.2.6..Exposure to environmental molecules and Alzheimer's Disease:

-Pesticides:

Exposure to pesticides seems strongly associated with the risk of AD. pesticides emerged as the strongest contributor to AD risk among the substances examined. Pesticides have been widely used in food production globally for decades. Despite regulatory measures, including banning the most toxic pesticides and setting maximum residue limits in food and water, the general population remains exposed to a variety of pesticides, often in mixtures that could pose cumulative hazards due to their similar modes of action or toxicity to the same target organs. Epidemiological studies indicate that occupational exposure, especially among pesticide applicators and farmers, correlates with increased rates of AD.

-Heavy Metals:

The evidence regarding Hg is slightly inconsistent, but associations are possible. Studies on As show potential links to AD risk, although inconsistencies exist between findings. Research on Cd presents contradictory results, yet suggests a possible association with AD. The evidence regarding Pb is conflicting and somewhat weaker compared to other substances, but possible associations with cognitive decline and AD risk have been reported. Occupational exposure to heavy metals remains a significant concern, highlighting the necessity of stringent safety procedures and protective measures at workplaces (100).

II.2.7.Impact of diet on Alzheimer's Disease risk:

-Western Diet and Alzheimer's Disease risk:

The Western diet, known for its high content of refined grains, sugar, unhealthy fats, and salt, along with low consumption of fruits and vegetables, is linked to various health issues, including obesity, cardiovascular diseases, and type 2 diabetes (101,102). This diet often includes high intake of ultra-processed foods, which contain hydrogenated oils, added sugars, saturated fats, and additives. These components disrupt the gut microbiome, leading to immune alterations and chronic inflammation (103). Furthermore, the excessive consumption of high glycemic index foods, saturated fats, and high sodium content contributes to conditions such as

hypercholesterolemia and insulin resistance, impairing vasoreactivity and endothelial integrity, thereby increasing the risk of Alzheimer's disease (AD) (104,105) (Figure 15).

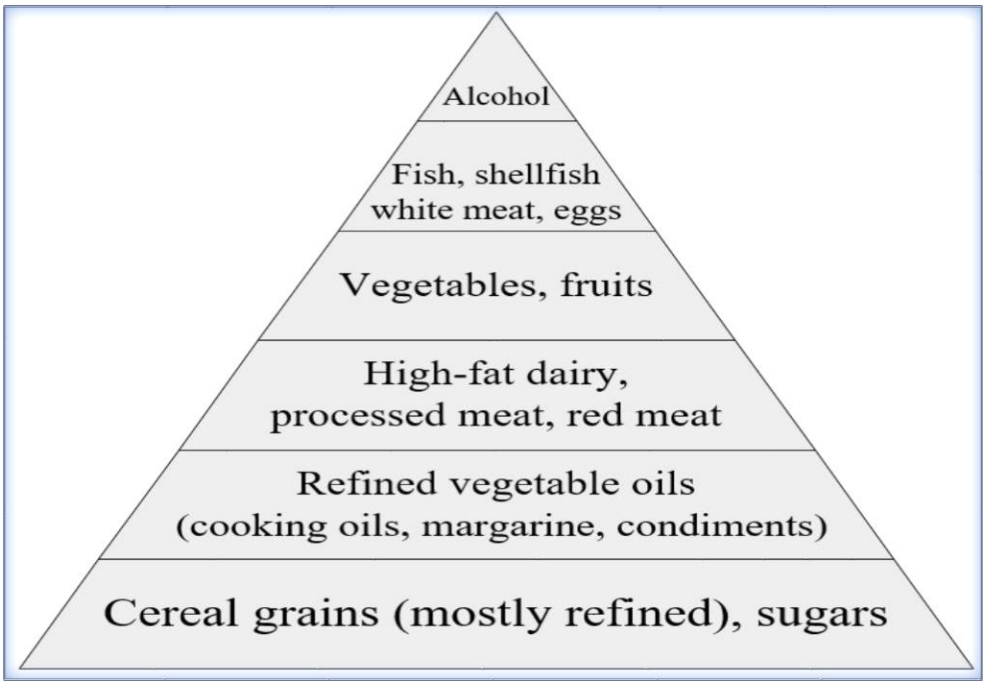

Figure 15 : The Western diet pyramid (106).

-Mediterranean Diet and Alzheimer's Disease risk:

The Mediterranean diet (MedD) emphasizes high consumption of olive oil, unrefined cereals, fruits, vegetables, and fish, with moderate dairy intake and low red meat consumption. This diet is associated with numerous health benefits, including reduced risk of cognitive decline and dementia. Studies have shown that adherence to the MedD is linked to a lower risk of conversion from mild cognitive impairment to dementia and a reduction in dementia incidence (107–110). The MedD has been shown to maintain brain health, lower cognitive decline risk, and improve cognition (111,112). However, some studies report inconsistent findings regarding its benefits, possibly due to differences in study populations and variations in dietary components and scoring systems (Figure 16).

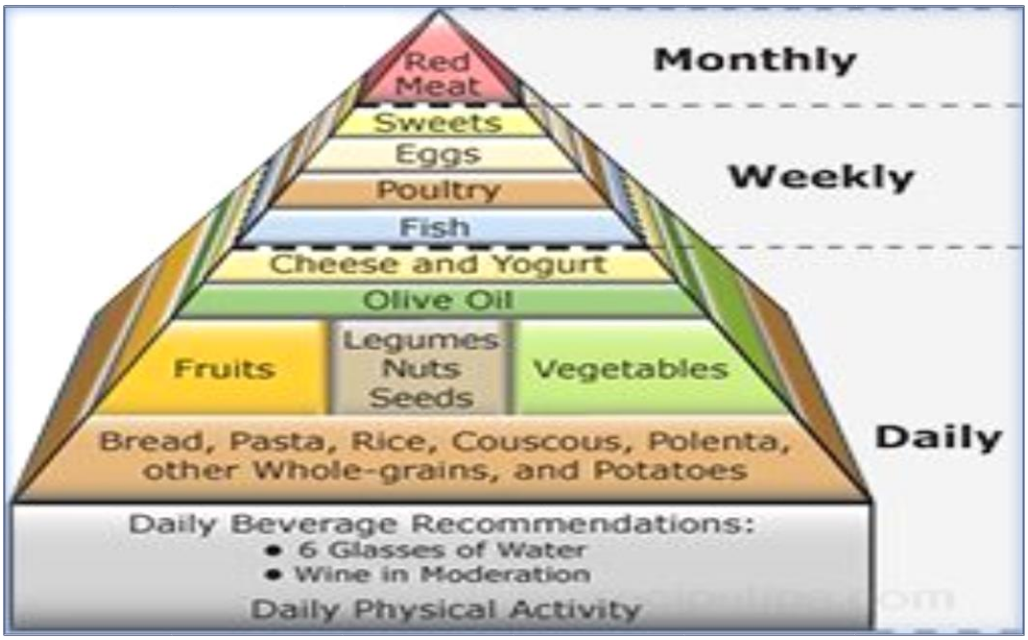

Figure 16 : The MedD pyramid (113).

II.3.Genetic factors:

Genetic risk factors and immunological implications:

Alzheimer's disease (AD) is a complex neurodegenerative disorder with both sporadic and hereditary forms. While the majority of AD cases are sporadic, accounting for approximately 90-95% of all cases, genetic factors play a significant role in disease pathogenesis. This section explores the genetic underpinnings of AD, focusing on mutations in the APP, PSEN1, and PSEN2 genes, the impact of the APOE ε4 allele on immune response and AD risk, and the interaction between genetic predispositions and the immune system.

-Mutations in APP, PSEN1, and PSEN2 Genes:

Since the 1930s, it has been recognized that early-onset AD (EOAD), which represents a rare form of AD (up to 5% of all cases), is fully genetically determined. However, it wasn't until the 1980s that three genes—APP, PSEN1, and PSEN2—were identified as responsible for EOAD (114). These rare mutations lead to the aggregation of amyloid proteins, driving the progression of early-onset AD.

-Impact of APOE ε4 allele on immune response and AD Risk:

APOE, a lipoprotein involved in lipid transport, was discovered in 1993 as the most significant genetic risk factor for late-onset AD. The APOE gene has three isoforms—APOE2, APOE3, and APOE4—with APOE4 being the most strongly associated with increased AD risk (115).

APOE modulates immune responses, exhibiting anti-inflammatory effects in various mouse models. Studies have shown that APOE knockout in primary microglia and astrocytes significantly enhances pro-inflammatory cytokine secretion from microglia and reduces anti-inflammatory cytokine release from both cell types (116). In the human brain, APOE is primarily produced by astrocytes, though its expression in microglia increases with aging and in response to amyloid and tau pathology (117) (Figure 17).

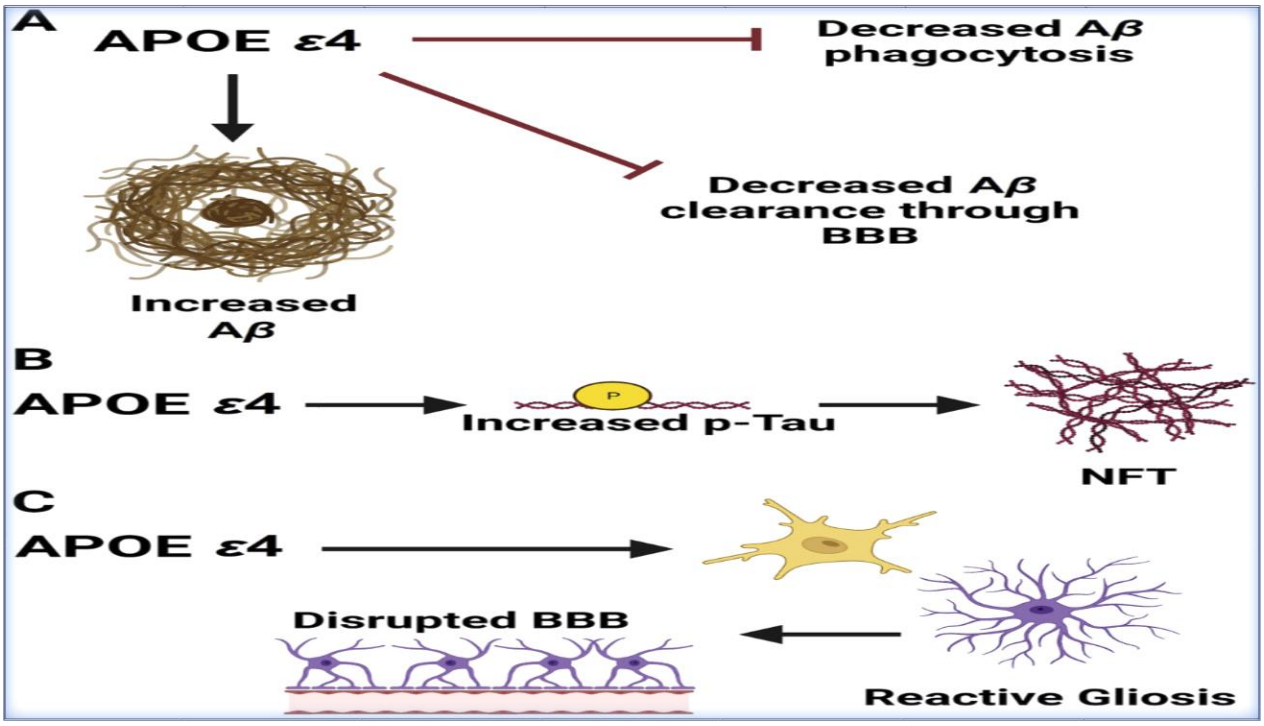

Figure 17 : Role of APOE in AD (118).

-The APOE4 isoform increases AD risk significantly**:** carrying one APOE4 allele raises AD risk by 3-4 times, while two alleles increase the risk by 9-15 times (119). The single amino acid difference between APOE3 and APOE4 alters the protein's conformation, affecting its interactions with receptors, lipids, and Aβ. APOE4 impacts AD development through various pathways, prominently involving inflammatory regulation. Lipid accumulation, a common feature in AD patients and mouse models, suggests that APOE4 may impair lipid transport and disrupt brain lipid homeostasis, inducing chronic inflammation and neurodegeneration (120).

-insulin signaling:APOE4 has been shown to inhibit insulin signaling and decrease brain glucose utilization, contributing to neuroinflammation and AD progression (121).

-APOE and TREM2: Recent studies suggest that APOE is a ligand for TREM2, an immune regulatory receptor on myeloid cells. APOE binding to TREM2 may switch microglia from a homeostatic to a neurodegenerative phenotype, highlighting the complex role of the APOE-TREM2 pathway in AD (122,123).

II.4.Chronic diseases :

II.4.1.Chronic inflammatory diseases and Alzheimer's Risk:

-the Link between chronic inflammatory diseases and Alzheimer's Disease:

Alzheimer's disease (AD) is more likely to develop in individuals with chronic diseases such as atherosclerosis, metabolic syndrome, and type 2 diabetes mellitus (T2DM). These conditions are characterized by systemic chronic inflammation, which may trigger the accumulation of amyloid β-protein (Aβ) in AD.

-The mechanisms by which systemic inflammation contributes to AD pathology:

-Atherosclerosis and Alzheimer's Disease:

Atherosclerosis, a chronic inflammatory disease of the arteries, involves the deposition of cholesterol and lipoproteins in the arterial wall, leading to atherosclerotic plaques and subsequent inflammation and calcification. Risk factors for atherosclerosis, such as age, dyslipidemia, hypertension, T2DM, smoking, and the presence of the apolipoprotein E4 (APOE4) allele, overlap with those of AD (124).

Research indicates that coronary artery stenosis due to atherosclerosis is more common in AD patients, with severity correlating with the number of amyloid plaques, neurofibrillary tangles (NFTs), and white matter atrophy in the brain. Additionally, the development of AD is often accompanied by cerebral atherosclerosis, which impairs Aβ clearance due to hypoxia (124). The pathogenesis of both atherosclerosis and AD involves inflammatory and immune responses, with an increased expression of C-reactive protein (CRP) and proinflammatory cytokines like IL-1 and IL-6 (125). The activation of the NLRP3 inflammasome plays a critical role in both conditions, promoting the production of proinflammatory cytokines IL-1β and IL-18 (126,127).

-Type 2 Diabetes Mellitus and Alzheimer's Disease:

Patients with T2DM have a higher risk of developing AD, with studies indicating a 65% increased risk compared to those without diabetes (128). Hyperglycemia and tissue hypoxia in T2DM lead to the accumulation of glycation end products, such as pentosidine and GLAP, which increase the expression of BACE1, promoting amyloidogenic APP metabolism and Aβ accumulation (129). Increased expression of RAGE receptors in the hippocampus and prefrontal cortex of diabetic AD models correlates with microglial activation and neuroinflammation (130,131). Hyperinsulinemia also reduces the availability of insulin-

degrading enzyme (IDE) for Aβ degradation, contributing to Aβ accumulation (132) (Figure 18).

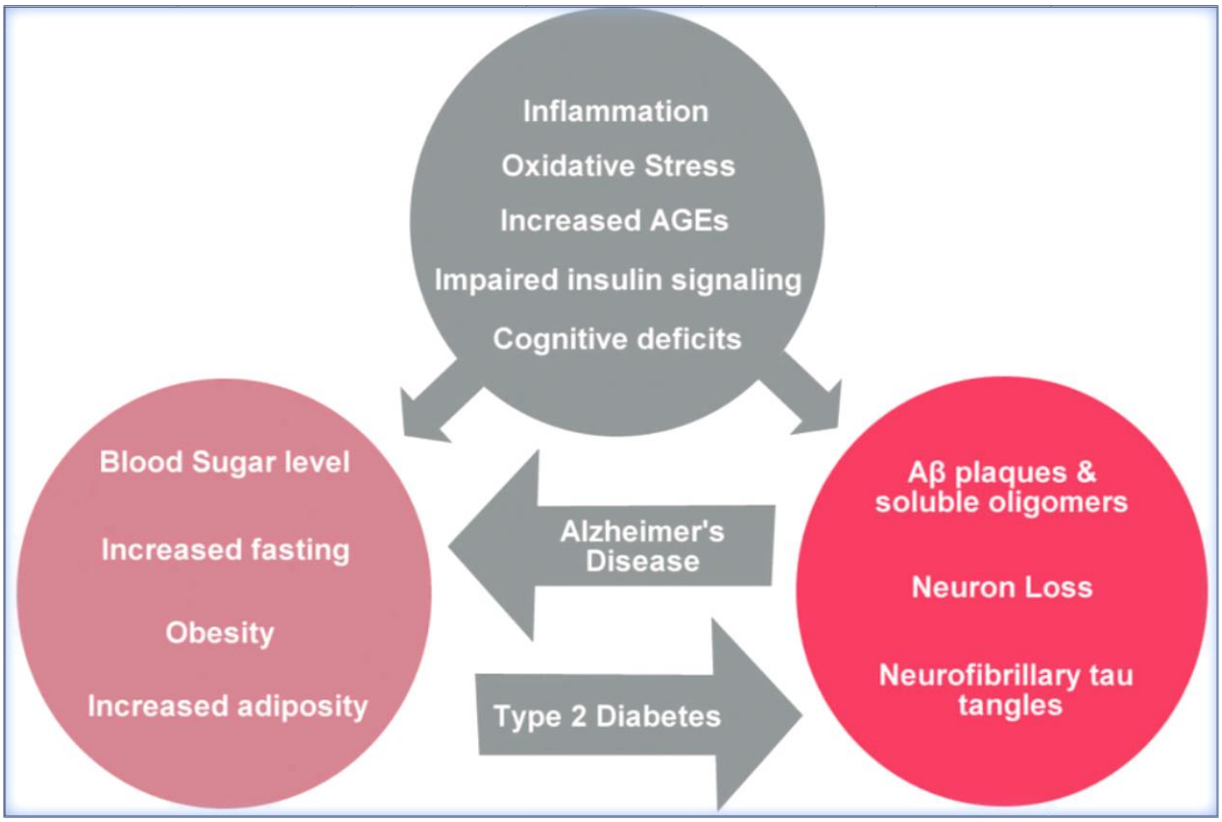

Figure 18 : T2DM and AD (133).

In summary, chronic inflammatory diseases such as atherosclerosis and T2DM contribute to AD pathogenesis through systemic inflammation, microglial activation, and impaired Aβ clearance. The inflammatory pathways involved include NF-κB, NLRP3, and others, leading to neurodegeneration and cognitive decline.

II.4.2.Depression and Alzheimer's Disease:

-Association between depression and AD risk:

Depression is commonly observed in individuals with Alzheimer's disease (AD) and is considered both a consequence and a potential risk factor for the disease. Depression and anxiety occur throughout the AD course due to both brain damage and psychosocial factors.

It has been associated with AD pathology, such as lower cerebrospinal fluid (CSF) Aβ42 and higher t-tau and p-tau levels. It is also linked to atrophy in brain regions including the insula, inferior frontal lobe, and limbic neural networks, as well as changes in the temporal and parietal regions, including the supramarginal, superior, and inferior temporal and fusiform gyri, right posterior cingulate and precuneus, locus coeruleus, and basal nucleus of Meynert (134).

II.4.3.Stress and Alzheimer's Disease:

-Association Between Stress and AD Risk:

Stress is a significant factor that exacerbates the pathogenesis of Alzheimer's disease (AD) in animal models. Studies have shown that stress can accelerate amyloid pathology, tau phosphorylation, and cognitive impairment in these models. While lifestyle changes that reduce stress have been suggested to prevent dementia, there is no conclusive evidence in humans. However, these findings indicate a potential link between stress and AD progression, warranting further investigation (135).

II.4.4.Impact of gut health on Alzheimer's Disease risk:

-Gut-Brain Axis and Alzheimer's Disease:

Alzheimer's disease (AD) is characterized by neurodegenerative cognitive dysfunction and memory loss, predominantly affecting older adults. The etiology of AD involves multiple factors, including neurofibrillary tangles (NFTs) and amyloid β-protein (Aβ) plaques, but emerging research highlights the significance of the gut-brain axis in AD development. Chronic intestinal inflammation, such as that seen in inflammatory bowel disease (IBD), has been linked to an increased risk of AD, suggesting a bidirectional communication pathway between gut microbes and the brain.

-Inflammatory Bowel Disease and Alzheimer's Disease:

Epidemiological studies have indicated that patients with IBD are more likely to develop AD compared to those without IBD. The gut-brain axis plays a crucial role in this relationship, where intestinal inflammation can lead to central nervous system (CNS) inflammation. Preclinical models have demonstrated that IBD exacerbates AD pathology, including the formation of Aβ plaques and tau tangles (136).

II.5.Oral health:

Oral Bacterial infections and Alzheimer's Disease:

-The link between oral bacterial infections and Alzheimer's Disease:

The dysregulated composition of the oral microbiota is closely associated with detrimental oral health outcomes and neuroinflammation, initiating neurodegeneration. Specifically, oral microorganisms produce virulence factors like gingipains, lipopolysaccharides, and outer membrane vesicles (OMVs), which mediate chronic periodontal inflammation and damage to periodontal support tissues. OMVs produced by Porphyromonasgingivalis may activate glial cells, leading to neuroinflammation and impaired memory function. Gingipains may propagate among neurons similarly to infectious diseases, directly damaging Tau proteins and activating human proteases associated with Tau proteins, contributing to AD pathology.

Inflamed periodontal tissues secrete pro-inflammatory cytokines (e.g., IL-1, IL-6, TNF-α), chemokines, and IL-8, alongside bacteria that sustain inflammation. These inflammatory mediators can enter circulation through inflamed capillaries, cross the blood-brain barrier (BBB), and access the central nervous system. Alternatively, they may disseminate to the brain via cranial nerves such as the olfactory nerve and trigeminal nerve, triggering inflammatory cascades, leading to neurodegeneration, brain atrophy, and cognitive decline. These processes suggest a potential association with AD development and progression, warranting further research (137).

III.The clinical profile of Alzheimer's disease

III.1.Diagnosis and symptoms of Alzheimer's Disease (AD)

Even though Alzheimer's disease cannot be cured, its progression can be slowed. Early diagnosis is crucial for effective management, as it helps patients maintain social connections and slows the disease's impact. Studies support the benefits of early detection.

III.1.1.Types of diagnosis:

-Etiological diagnosis: Identifies Alzheimer's disease as the root cause of symptoms by focusing on the presence of amyloid-beta plaques and tau tangles in the brain, ruling out other potential causes of dementia.

-Positive diagnosis: Confirms Alzheimer's disease through:

Clinical Assessments: Utilizing tools such as the Mini-Mental State Examination (MMSE) and other cognitive tests to Search for these indicative clinical signs: Memory Issues:

1. Changes in personality and/or behavior
2. Forgetting recent events
3. Language difficulties
4. Trouble performing usual tasks
5. Misplacing everyday items
6. Disorientation in time and space
7. Difficulty with abstract thinking
8. Impaired judgment

Biological Tests: Measuring biomarkers in cerebrospinal fluid (CSF) or blood, such as amyloid-beta and tau protein levels, to support the diagnosis.

Radiological Imaging: Employing PET scans to detect amyloid-beta deposits and tau pathology, as well as MRI scans to assess brain atrophy and structural changes.

-Differential diagnosis: Differentiates Alzheimer's disease from other conditions with similar symptoms, ensuring that amyloid-beta and tau-related abnormalities are specifically identified to distinguish it from other forms of dementia.

A proper diagnosis may not be achieved during the first specialized consultation. Given its profound impact on patients and their families, it must be precise (138).

III.2.Stages of Alzheimer's Disease (AD):

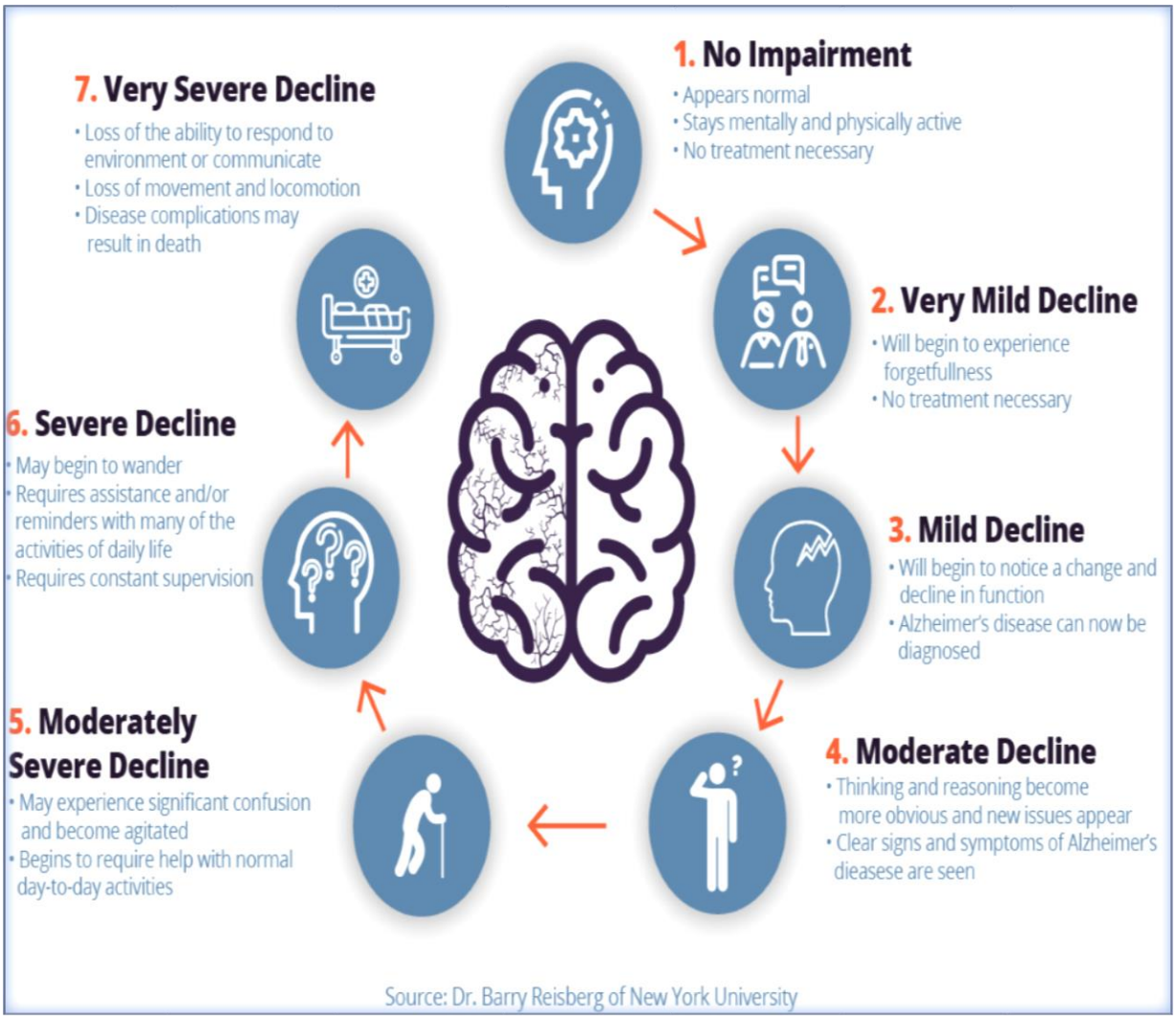

Figure 19 : stages of alzheimer's disease (139).

III.3.Therapeutic management of Alzheimer's Disease (AD)

While Alzheimer's disease cannot be cured, its progression can be managed to improve patients' quality of life. In Algeria, both pharmacological and non-pharmacological treatments are utilized.

III.3.1.Pharmacological treatments:

1. Cholinesterase Inhibitors**:**

    a. Donepezil (Aricept)
    b. Rivastigmine (Exelon)
    c. Galantamine (Razadyne) These drugs boost acetylcholine levels in the brain to help with memory and cognitive function.

2. NMDA Receptor Antagonists**:**

   Memantine (Namenda) This medication regulates glutamate activity to support learning and memory.

3. Combination Therapy**:**

   Memantine and Donepezil together to enhance symptom management.

III.3.2.Non-Pharmacological treatments:

1. Cognitive Stimulation : Engages patients in activities to boost memory and problem-solving skills.
2. Physical Exercise**:** Encouraged to maintain overall health and improve mood.
3. Dietary Management **:** Emphasizes a balanced diet, often incorporating the Mediterranean diet.
4. Social Engagement **:** Programs to keep patients socially active, which can slow cognitive decline (137)

III.3.3.Monitoring the disease :

The management of Alzheimer's disease involves a multidisciplinary team. Additionally, various organizations offer support and facilities for patient care. Patient associations also provide information and support for both patients and caregivers.

Practical Section

I.Materials and Methods:

I.1.Study design:

This observational, cross-sectional study aimed to identify the prevalence and impact of various lifestyle and environmental risk factors for Alzheimer's disease (AD) in an elderly population. The study was conducted in collaboration with the National Algerian Association of Alzheimer's Disease, which ensured ethical approval and consent from participants.

I.2.Participants:

The study included 29 elderly individuals aged between 67 and 93 years. Participants were selected through random sampling and provided informed consent to participate in the study. The National Algerian Association of Alzheimer's Disease facilitated the recruitment process and obtained the necessary ethical approvals.

I.3.Data collection:

Data were collected through a combination of phone interviews and face-to-face interactions. A standardized survey was used to gather information, which included both standardized questions and open-ended responses. The survey covered a comprehensive list of risk factors, including:

1) Demographic information (age, sex)
2) Lifestyle factors (obesity, smoking, alcohol consumption, diet, exercise, sleep patterns)
3) Social factors (educational level, economic status, sociability, stress)
4) Health status (hypertension, diabetes, hypercholesterolemia, depression, oral health)
5) Environmental exposures (chemical substances)
6) Family history of Alzheimer's disease
7) Gut health
8) General health conditions (any other diseases)

For some participants, relevant medical records were reviewed to verify the information provided, particularly regarding their history with diseases such as hypertension, diabetes, and hypercholesterolemia. These records were obtained with the participants' consent and were used to supplement self-reported data.

I.4.Data analysis:

The data collected were analyzed using descriptive statistics to summarize the prevalence of each risk factor among the participants. Graphs and charts were generated using SPSS.

I.5.Ethical considerations:

Ethical approval for the study was obtained from the National Algerian Association of Alzheimer's Disease. Participants were fully informed about the study's purpose and their right to withdraw at any time without any consequences. All participants provided informed consent before participating in the study.

I.6.Data handling and confidentiality:

Data confidentiality was maintained by storing all responses and medical records securely in the Google Form, which is protected by encryption and access controls. Only authorized personnel involved in the study had access to the data. All identifying information was anonymized to protect participants' privacy.

II.Result and Discussion:

II.1.Demographic factors :

II.1.1.Age Distribution of survey respondents:

The mean age is higher than the median and mode, indicating a right-skewed age distribution (Figure 20).

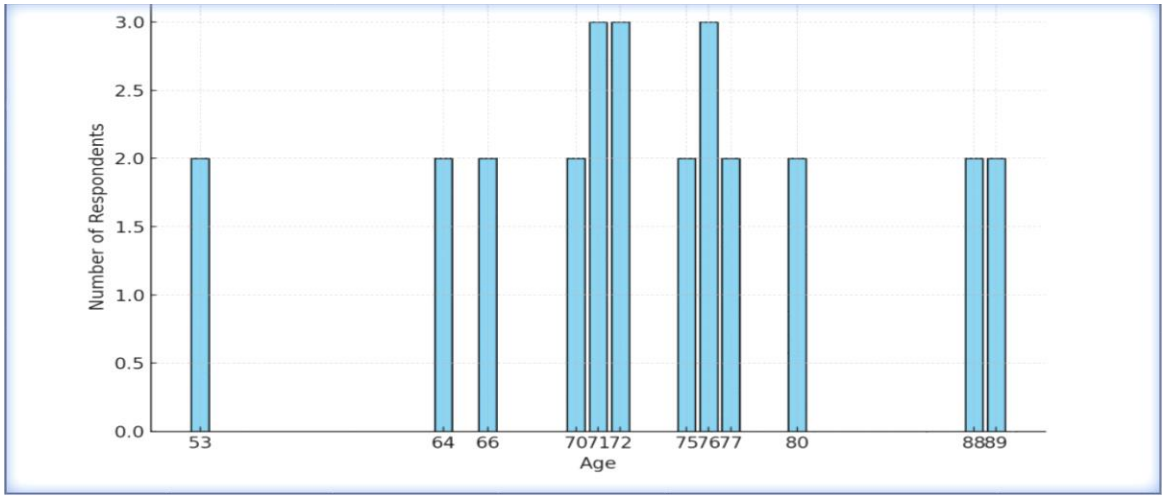

Figure 20 : Distribution of ages among the surveyed respondents

In a study conducted over 17 years with a cohort of 5,765 participants, the mean age at baseline was 64 years. Alzheimer's disease (AD) diagnoses occurred on average 10.4 years after baseline (140).

The comparative analysis shows that the mean age of survey respondents (73.37 years) aligns closely with the average age of Alzheimer's diagnosis (74.4 years) reported in the longitudinal study. This suggests that the survey population is within the typical age range for Alzheimer's disease onset, supporting the relevance of our survey data in understanding age-related risk factors for Alzheimer's disease.

An emerging theory is that Age is a risk factor for Alzheimer's disease due to the diminished efficacy of immune cells in clearing senescent cells, leading to an increase in SASP-secreting cells and chronic inflammation. Additionally, primary genomic disturbances, mitochondrial dysfunction, and stem cell depletion exacerbate cellular aging and tissue degradation, contributing to AD pathogenesis (86).

II.1.2.Sex distribution of survey respondents:

The percentage of female respondents was significantly higher than that of male respondents.(Figure 21)

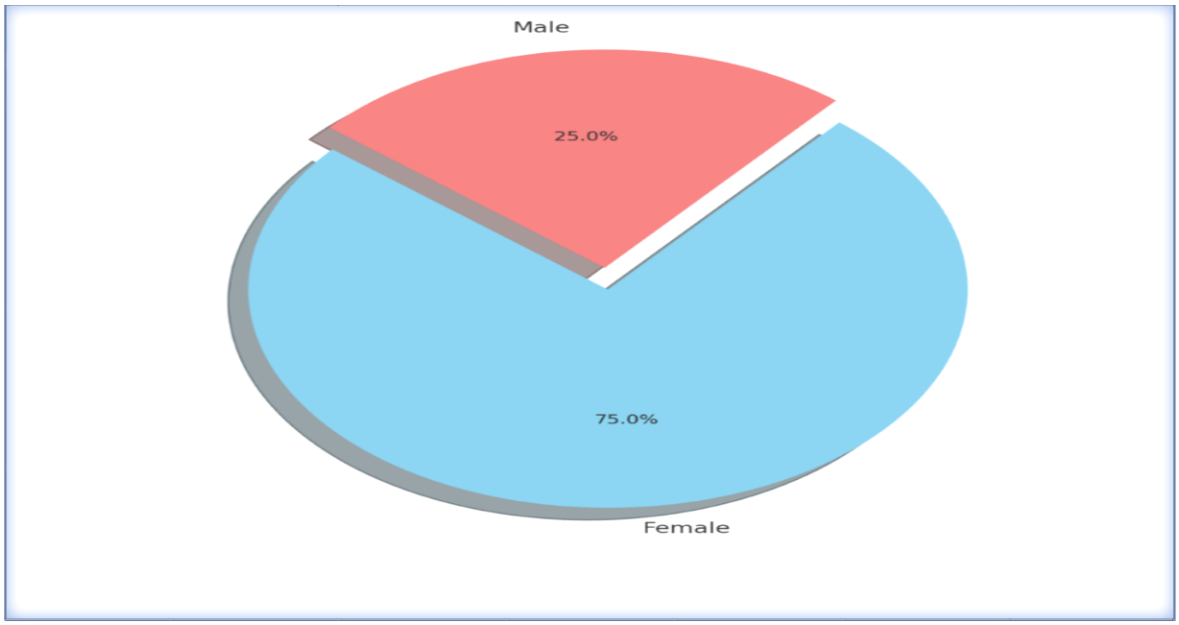

Figure 21 : Distribution of sexes among the surveyed respondents.

A global study on dementia prevalence found that the condition is more common in women than in men, and this pattern is expected to continue through 2050. In 2019, women had a higher prevalence of dementia than men, with a female-to-male ratio of 1.69. This ratio is projected to be 1.67 in 2050. The prevalence of dementia increases with age, doubling approximately every five years. By 2050, the prevalence among those aged 85 years and older is expected to be 23.5% in men and 30.5% in women (141).

The higher percentage of female respondents (72.4%) in our survey aligns with global trends showing a higher prevalence of dementia among women.

It is proposed that the female sex is a risk factor for Alzheimer's disease due to the decline in estrogen levels during peri- and post-menopause, which disrupts brain glucose metabolism and increases chronic inflammation. This hormonal change leads to impaired mitochondrial function and increased oxidative stress, contributing to neurodegeneration (90).

II.2.Lifestyle factors :

II.2.1.Educational level of survey respondents:

The highest percentage of respondents were illiterate, followed by those with secondary education, primary education, and then higher education (Figure 22).

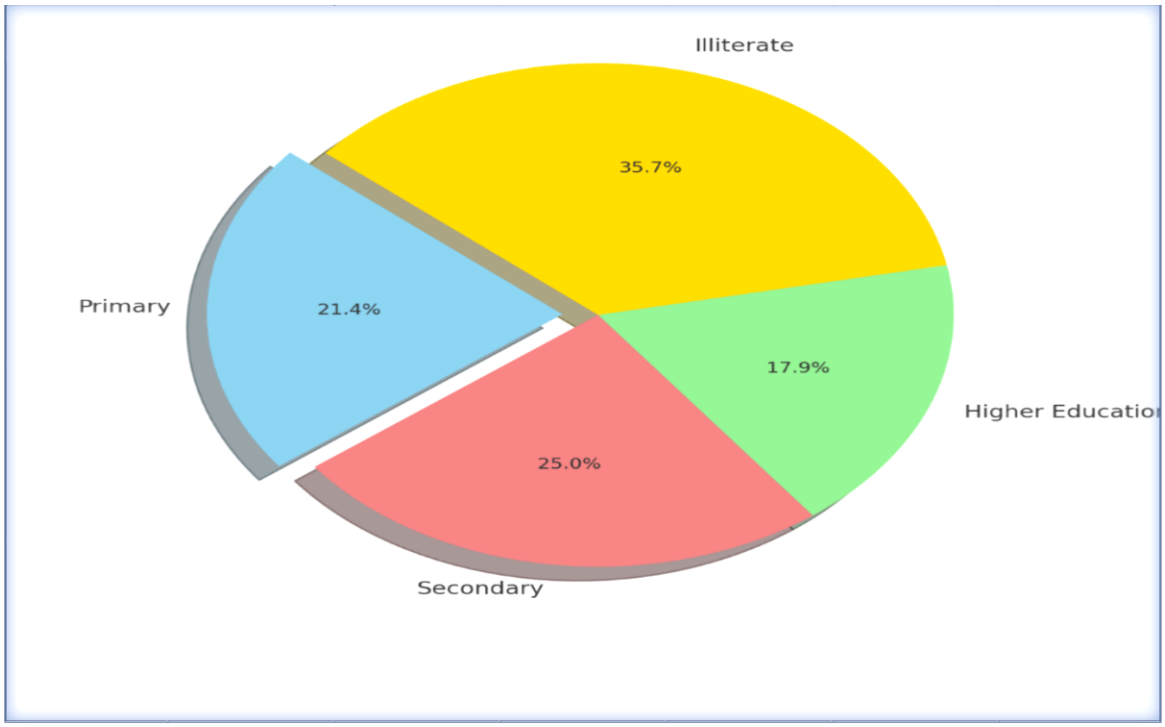

Figure 22 : Educational levels attained by the surveyed respondents.

A meta-analysis indicated that individuals with less education in early life (<45 years) have a relative risk of 1.6 (95% CI: 1.3–2.0) for developing dementia compared to those with higher education. This suggests that lower educational attainment significantly increases the risk of dementia (142).

In our study, 21.4% of respondents had primary education, 25.0% had secondary education, 17.9% had higher education, and 35.7% were illiterate. These findings are consistent with the meta-analysis, indicating that an important proportion of respondents with lower educational levels aligns with the increased risk of dementia observed in the literature. This supports the notion that higher education may be protective against dementia.

The higher percentage of illiterate respondents suggests a potential link between lower educational attainment and increased Alzheimer's disease risk. Lower education may lead to fewer cognitive reserves and greater vulnerability to neurodegenerative processes (142).

II.2.2.Social life of respondents:

The majority of respondents were social, with only a small percentage being isolated (Figure 23).

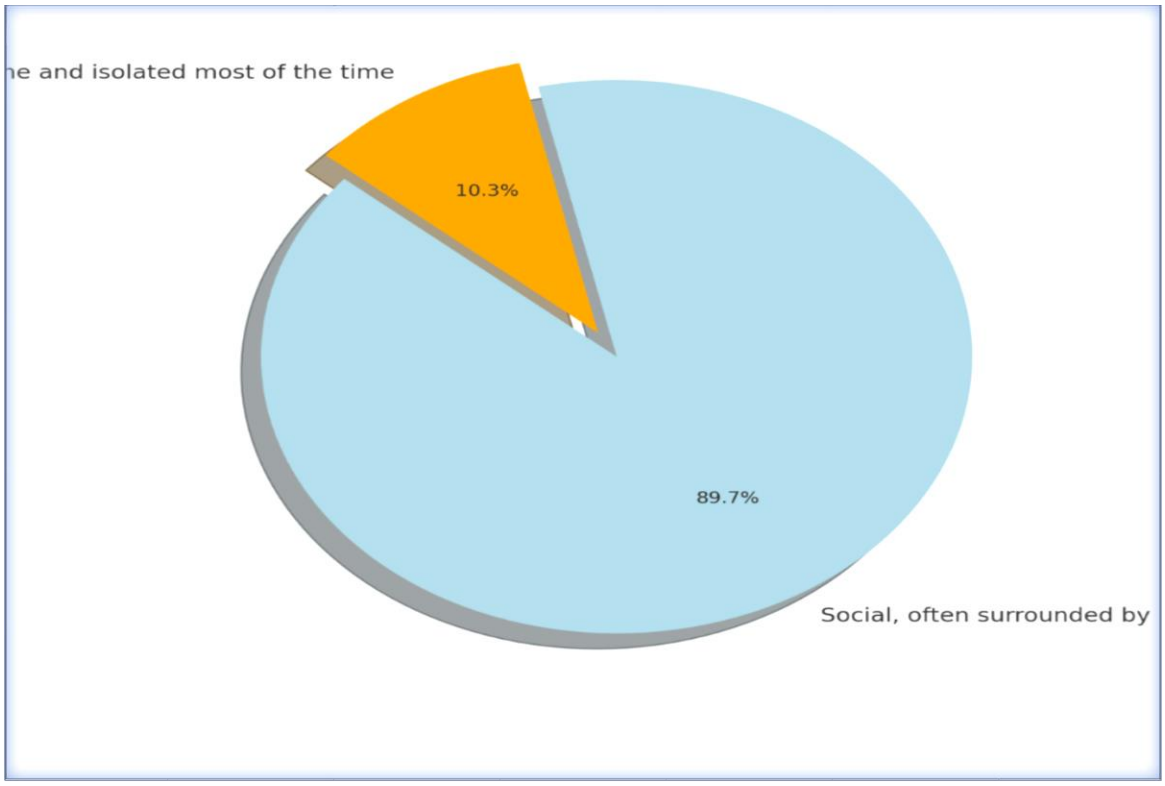

Figure 23 : Social engagement levels among the surveyed respondents.

Low frequency of social contacts has been identified as a significant risk factor for developing dementia. An analysis of eight studies involving 1,122 cases showed that individuals with low social interaction have a 1.57 times higher risk (RR = 1.57) of developing any form of dementia compared to those with more frequent social contacts. This association falls within a 95% confidence interval of 1.32 to 1.85, indicating a strong and statistically significant link. The evidence is classified as class I, with a medium quality rating according to the AMSTAR evaluation

Our findings show that 89.7% of respondents are social, which does not align with the study. The high level of social engagement among our respondents contrasts with the risk factor identified in the study, suggesting that other factors may be influencing alzheimer's risk in our Algerian population (143).(Figure 22)

II.2.3.Respondents who smoke:

The majority of respondents do not smoke, with only a small percentage being smokers (Figure 24).

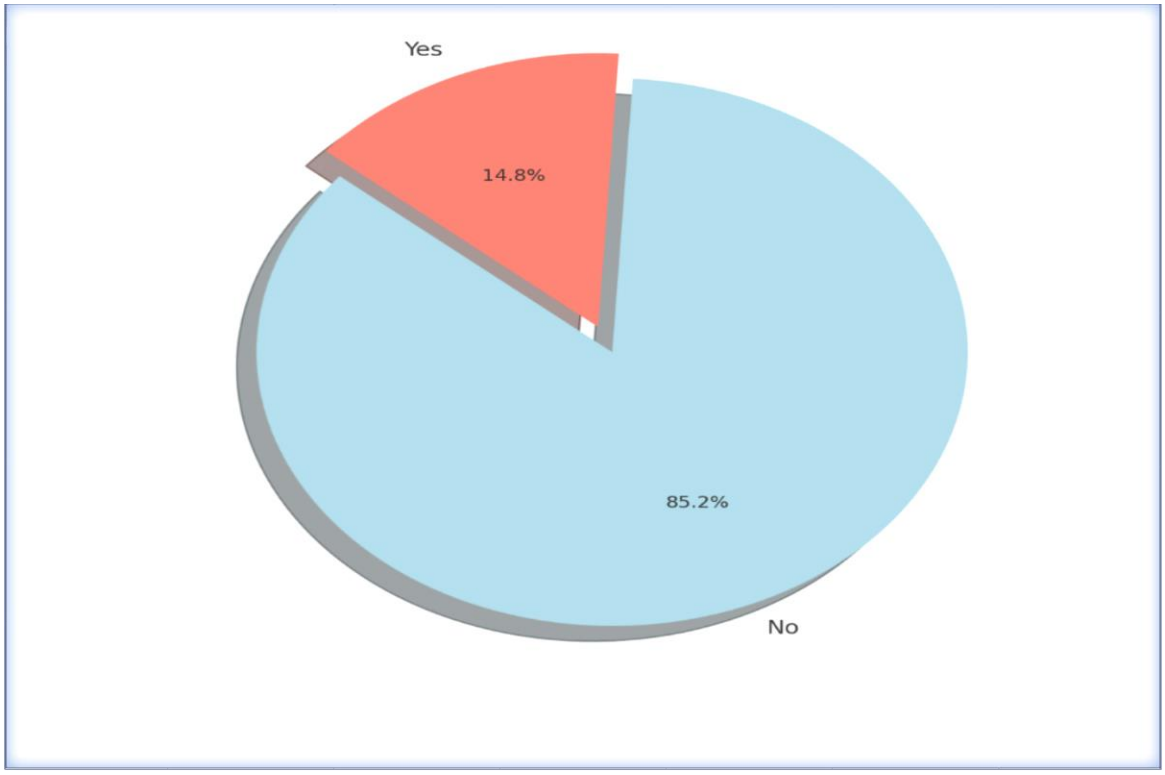

Figure 24 : Percentage of respondents who smoke versus those who do not.

A meta-analysis of 19 prospective studies found that current smokers had a relative risk of 1.79 (95% CI: 1.43, 2.23) for developing Alzheimer's disease (144).

In our study, 85.2% of respondents do not smoke, while 14.8% are current smokers. Although 14.8% is a relatively small percentage, the meta-analysis supports that smoking significantly increases the risk of Alzheimer's disease. Thus, even this smaller proportion of smokers can have a substantial impact on the incidence of Alzheimer's disease in the population.

A plausible hypothesis is that smokers have a substantially higher risk of developing AD, especially those carrying the APOE ε4 allele, which further exacerbates their risk. This suggests that the low percentage of smokers among respondents may reduce the overall risk of AD in this population (96).

II.2.4.Respondents who drink alcohol:

All respondents in this study don't drink any alcohol (Figure 25).

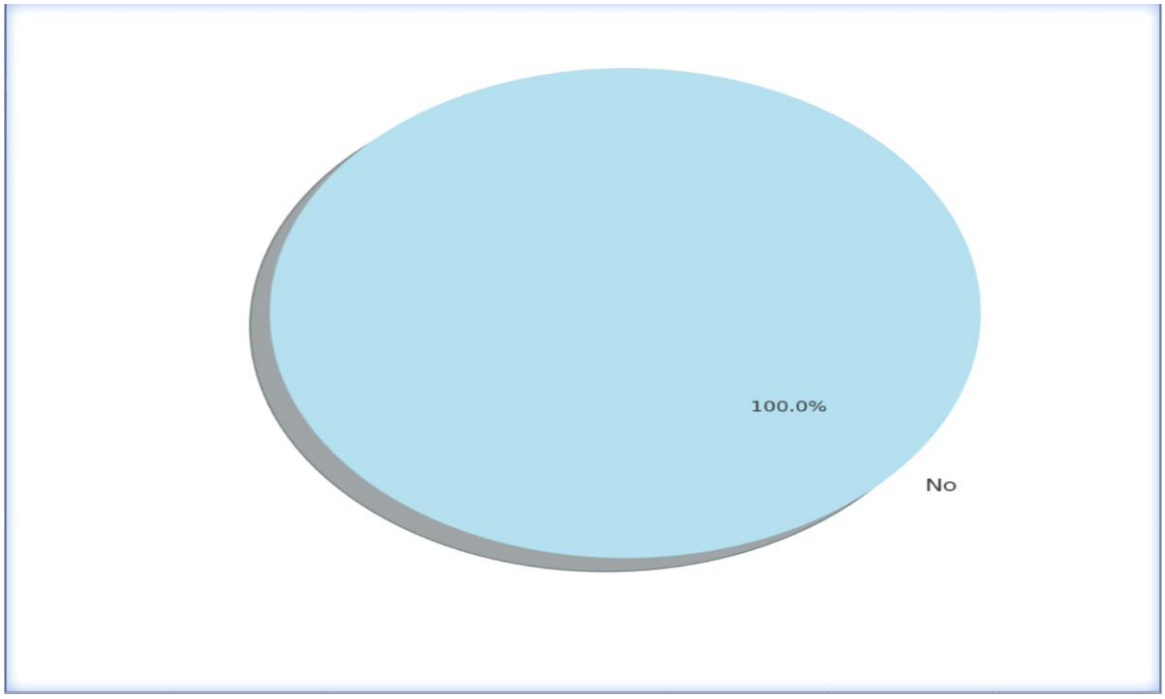

Figure 25 : Alcohol consumption status of the surveyed respondents.

In A study involving 31,624,156 adults discharged from French hospitals found that alcohol use disorders were a significant modifiable risk factor for dementia, including Alzheimer's disease. The adjusted hazard ratio for dementia onset due to alcohol use disorders was 3.34 for women and 3.36 for men, indicating a strong association between alcohol use and increased dementia risk (145).

In our study, 0% of respondents reported alcohol consumption. This significant difference underscores the absence of alcohol-related risk for Alzheimer's disease in our Muslim population which generally do not consume alcohol

II.2.5.Respondents exposed to neurotoxic chemicals :

A significantly higher percentage of respondents were not exposed to neurotoxic chemicals compared to those who were exposed (Figure 26).

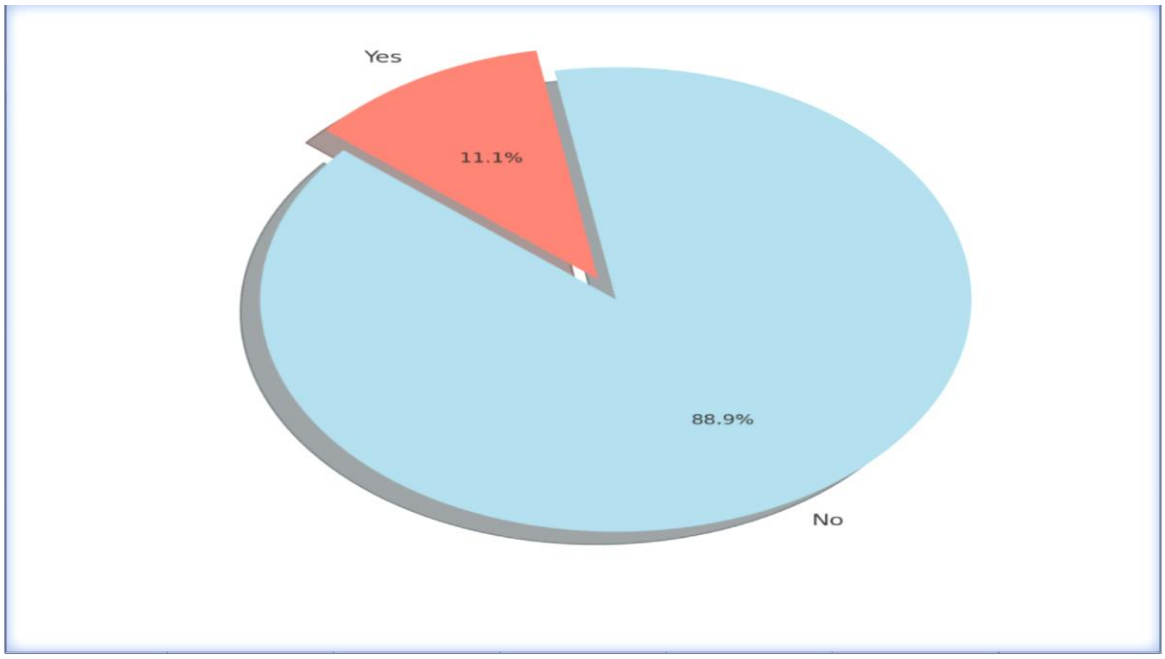

Figure 26 : Percentage of respondents exposed to neurotoxic chemicals.

Evidence suggests that lifelong exposure to pesticides increases the risk of Alzheimer's disease (AD), with a meta-analysis showing an odds ratio (OR) of 1.34. However, information on the impact of other neurotoxic chemicals on AD risk remains limited and inconsistent. Further high-quality studies are required to confirm these associations and explore the effects of various toxins (146).

Our findings show that 11.1% of respondents have been exposed to neurotoxic chemicals, which aligns with the article's suggestion that exposure to pesticides is associated with an increased risk of Alzheimer's disease. However, the limited and inconsistent information on other neurotoxic chemicals calls for more comprehensive studies to confirm these associations and understand the broader impacts of various toxins on Alzheimer's disease risk.

it’s suggested that The higher percentage of respondents not exposed to neurotoxic chemicals is advantageous, as exposure to pesticides and heavy metals is linked to increased Alzheimer's disease risk through neurotoxic mechanisms (100).

II.2.6.Sleep quality of respondents:

A higher percentage of respondents reported good sleep quality compared to those with excellent, average, or poor sleep quality (Figure 27).

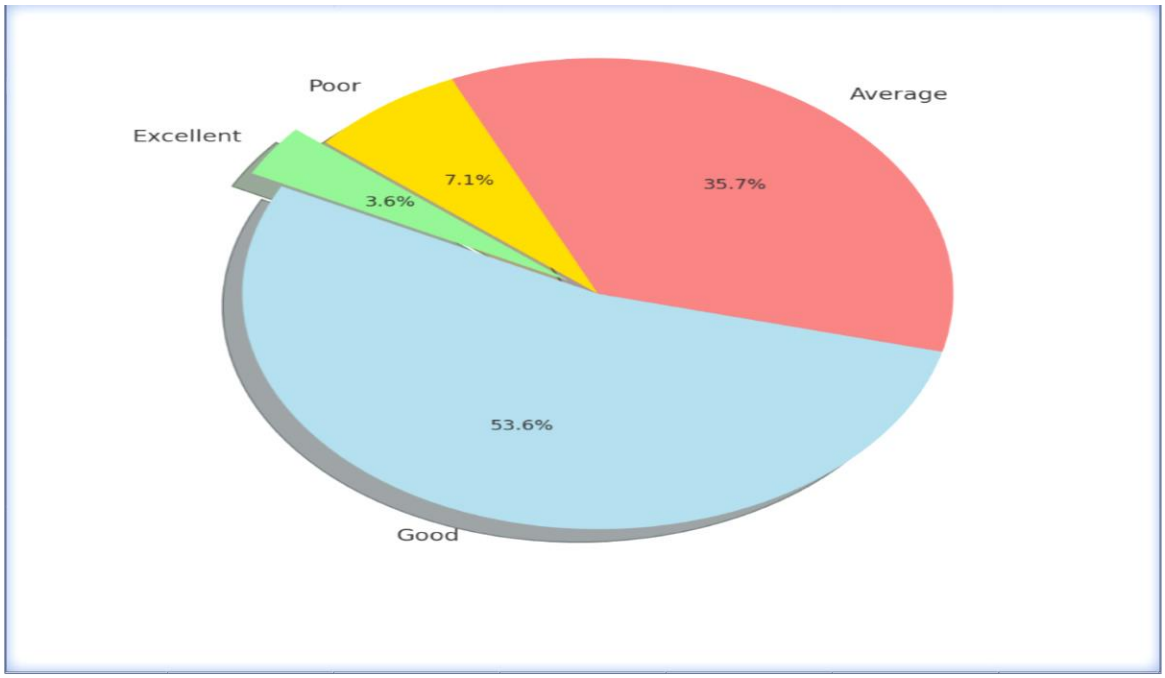

Figure 27 : Self-reported sleep quality among the surveyed respondents.

Recent studies indicate limited evidence for a causal relationship between sleep traits and Alzheimer's disease (AD) risk. However, there is suggestive evidence that self-reported daytime napping is associated with a lower risk of AD, with an odds ratio (OR) of 0.70 and a 95% confidence interval (CI) of 0.50-0.99. Other sleep traits, such as accelerometer-measured 'eveningness', sleep duration, and self-reported daytime sleepiness, had similar ORs but were less precisely estimated. These findings suggest that certain sleep behaviors may influence AD risk, although further research is needed to confirm these associations (147).

Our findings on sleep quality show that the majority of respondents report good or average sleep quality. This does not align directly with the study, which suggests that specific sleep behaviors, such as daytime napping, may lower the risk of Alzheimer's disease. The discrepancies highlight the need for further research to better understand the role of sleep in Alzheimer's disease risk, as our survey did not specifically measure these particular sleep traits.

A possible explanation is that Sleep disturbances accelerate Aβ deposition and other AD-related changes in the brain, such as increased phosphorylated tau and toxic Aβ species, contributing to AD progression (99).

II.2.7.Diet of respondents:

A significantly higher percentage of respondents consumed fatty foods and not much healthy stuff compared to those who ate balanced meals (Figure 28).

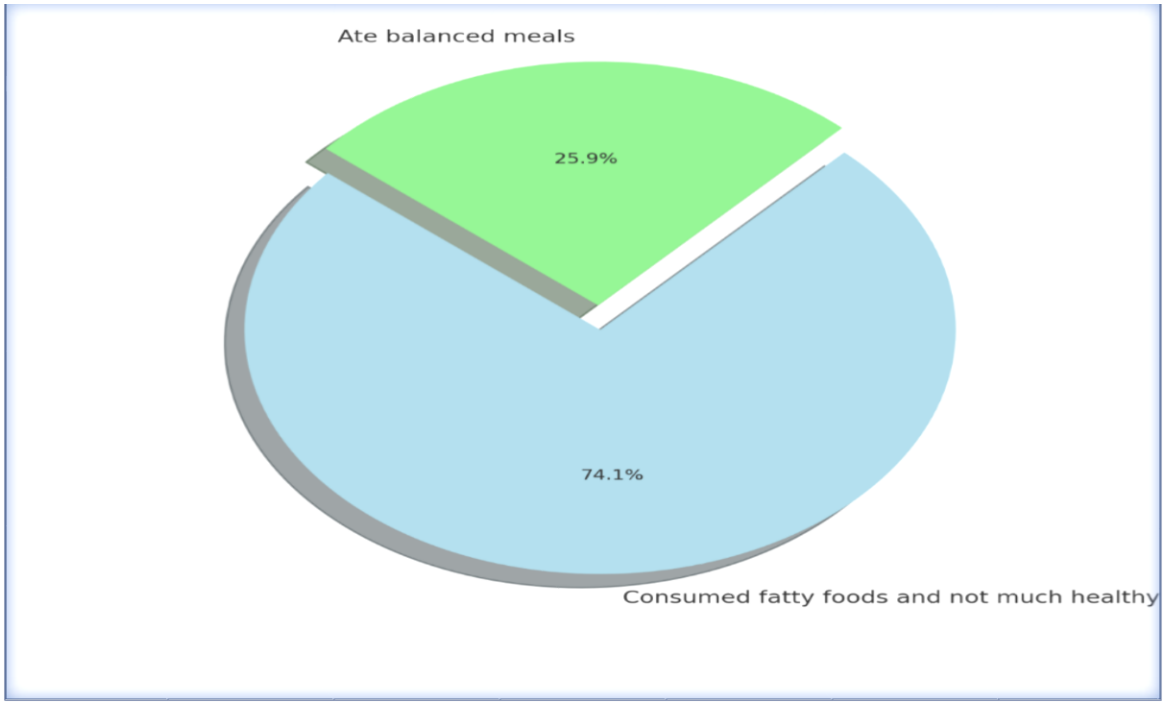

Figure 28 : The relationship between different dietary habits and the risk of Alzheimer's disease among respondents.

A 2015 meta-analysis identified a healthful dietary pattern as a significant modifiable risk factor for Alzheimer's disease, with a risk ratio (RR)/odds ratio (OR) of 0.45 (95% CI: 0.23–0.61), indicating that a healthy diet could reduce the risk of developing Alzheimer's by more than half (148).

Our study's findings align with the 2015 meta-analysis, which identified a healthful dietary pattern as significantly reducing the risk of Alzheimer's disease. The observed dietary habits in the study population suggest a potential increased risk of Alzheimer's disease.

Bad dietary habits might contribute to Alzheimer's disease risk by disrupting the gut microbiome, leading to immune alterations and chronic inflammation. These habits also cause hypercholesterolemia and insulin resistance, impairing vasoreactivity and endothelial integrity, which increases the risk of Alzheimer's disease. Conversely, good dietary habits support brain health, reduce inflammation, and lower the risk of cognitive decline and dementia (107–110), (104,105).

II.2.8.Obesity Status of Survey Respondents:

A higher percentage of respondents were not obese compared to those who were obese (Figure 29).

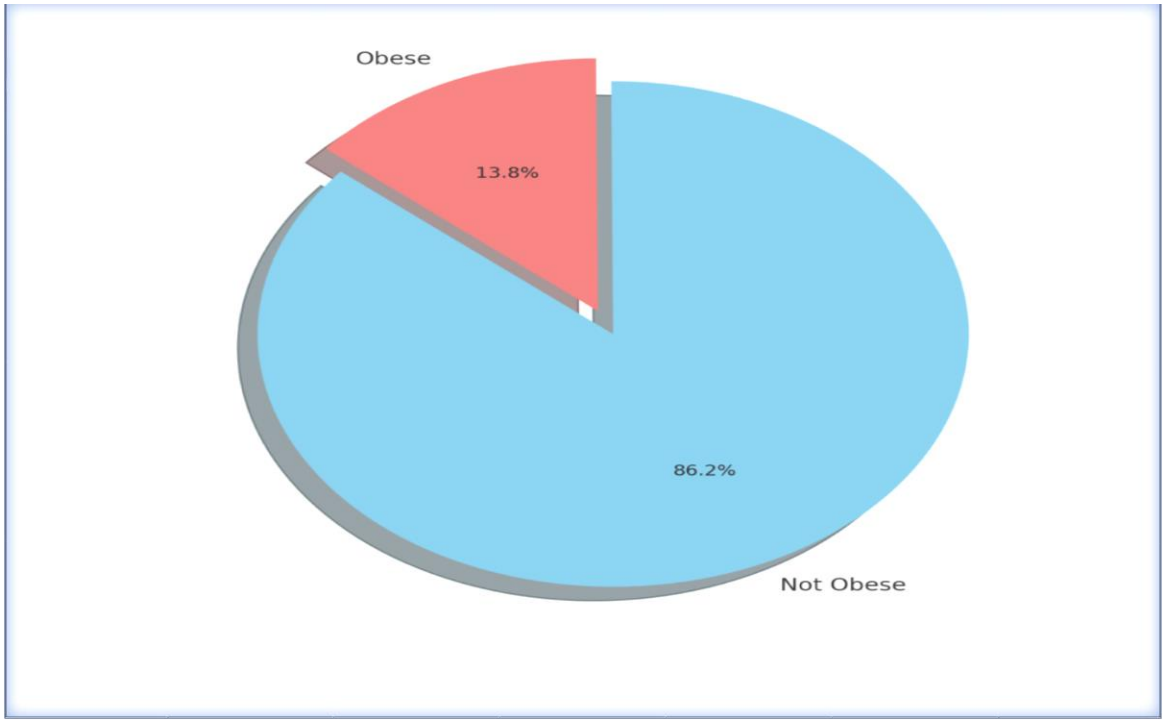

Figure 29 : participants with and without midlife obesity

A meta-analysis reviewed 1,612 abstracts and found that being obese before the age of 65 was positively associated with incident dementia, with a risk ratio (RR) of 1.41 (95% CI: 1.20-1.66). Conversely, obesity in those aged 65 and over was associated with a reduced risk of dementia, with an RR of 0.83 (95% CI: 0.74-0.94) (149).

In our study, 86.2% of respondents reported not being obese in midlife, while 13.8% reported being obese in midlife. This prevalence is consistent with the literature, indicating that midlife obesity is a probable risk factor for dementia, supporting the findings of increased dementia risk associated with midlife obesity.

A higher percentage of respondents were not obese compared to those who were obese, which is beneficial. Obesity contributes to Alzheimer's disease risk through mechanisms like chronic inflammation, insulin resistance, and disrupted lipid metabolism, with elevated levels of proinflammatory markers such as CRP, IL-6, and TNF-α. Additionally, obesity is linked to cardiovascular diseases and type 2 diabetes, further increasing AD risk (91).

II.3. Chronic Diseases :

II.3.1.Conditions diagnosed before Alzheimer's disease diagnosis:

A significant portion of respondents reported having high blood pressure, while smaller percentages reported high cholesterol and diabetes (Figure 30).

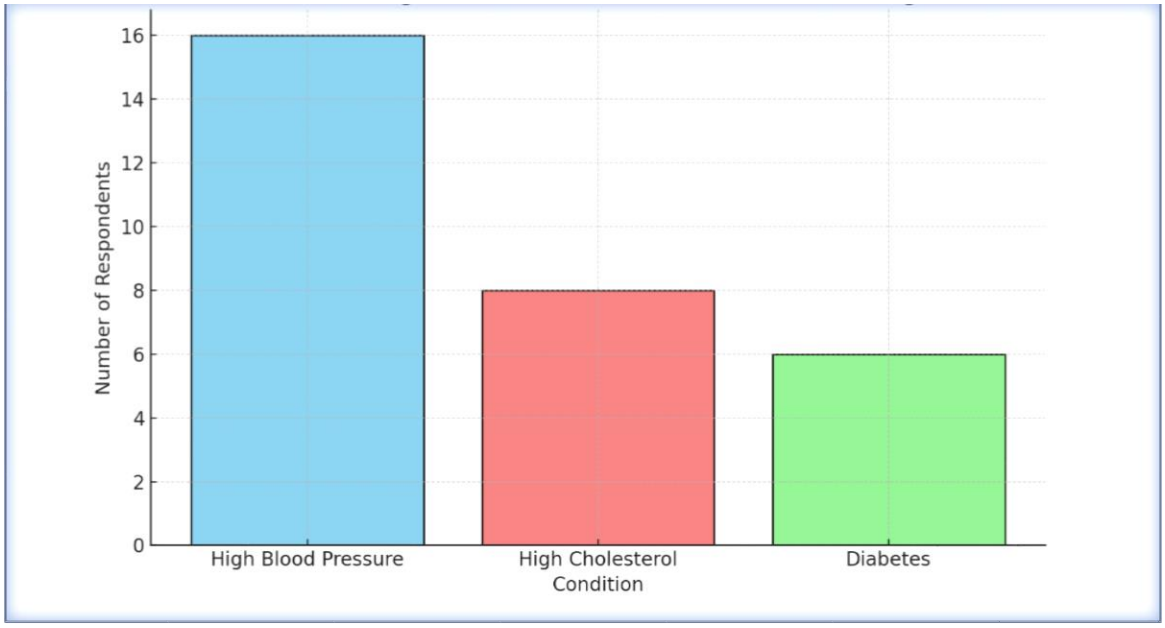

Figure 30 : Percentage of respondents with conditions diagnosed before Alzheimer's disease.

Hypertension and Alzheimer's Disease:

A study found that midlife systolic hypertension (HR 1.57, 95% CI 1.05-2.35) and persistence into late life (HR 1.96, 95% CI 1.25-3.09) were associated with an elevated risk of dementia. Additionally, individuals with low to normal blood pressure (≤140/90 mm Hg) in midlife who experienced a steep decline in systolic blood pressure later had a more than two-fold increased risk of dementia (HR 2.40, 95% CI 1.39-4.15) (150).

In our study, 53.3% of respondents had high blood pressure. These findings align with the literature, indicating that a large proportion of our participants are at an elevated risk for dementia due to hypertension. This emphasizes the importance of managing blood pressure to mitigate dementia risk.

Diabetes and Alzheimer's Disease:

In A comprehensive analysis of 14 studies involving 2,310,330 individuals and 102,174 dementia cases found that diabetes was associated with a 60% increased risk of any dementia in both sexes (151).

In our study, 20.0% of respondents had diabetes. This aligns with the literature, indicating that diabetes might increase the risk of developing dementia. Our findings support the need for effective diabetes management to potentially reduce dementia risk.

Cholesterol and Alzheimer's Disease:

A 2019 study reported a high summary exposure value (SEV) for high LDL cholesterol, with an SEV of 32.44 (95% uncertainty interval: 29.49 to 35.57). SEVs measure risk exposure on a 0 to 100 scale, where 100 represents maximum population risk and 0 represents minimum risk, indicating significant population exposure to high LDL cholesterol and its associated risks (152).

The presence of high cholesterol in 26.7% of our survey respondents highlights a possible risk factor for Alzheimer's disease. However, despite the association between high cholesterol and increased AD risk, current research does not support a protective effect of statins against Alzheimer's, underscoring the complexity of managing AD risk factors.

Hypertension and high cholesterol might contribute to AD by promoting systemic inflammation, vascular damage, and impaired amyloid β-protein (Aβ) clearance.

Diabetes increases AD risk through hyperglycemia and tissue hypoxia, leading to advanced glycation end products and reduced insulin-degrading enzyme availability, which promote Aβ accumulation and neuroinflammation (132).

II.3.2.Gut health of respondents:

A higher percentage of respondents reported having no gut issues compared to those who did (Figure 31)

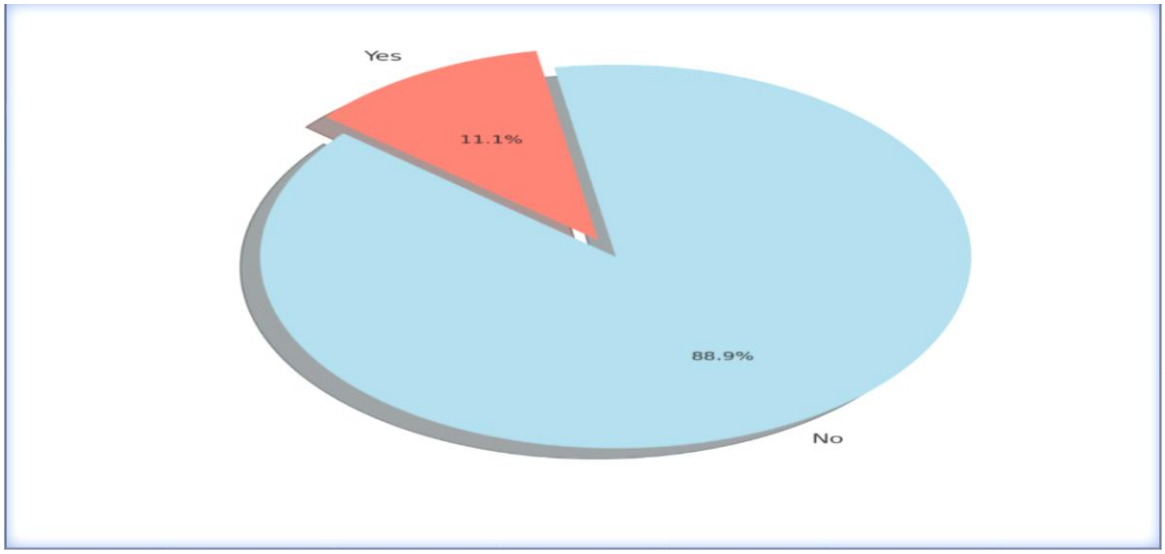

Figure 31 : Percentage of respondents with and without gut issues.

A study of 88,985 patients with inflammatory bowel disease (IBD) found that those with ulcerative colitis (UC) and Crohn's disease (CD) had a higher risk of developing dementia. UC patients showed a slight increase in the risk of all-cause dementia and Alzheimer's disease, while CD patients had a higher risk of all-cause dementia and frontotemporal dementia. This highlights a connection between gut health and cognitive decline, emphasizing the importance of managing IBD to potentially reduce the risk of dementia (153)

Our survey indicates that 11.1% of respondents have gut issues, not exactly aligning with studies showing that inflammatory bowel diseases like ulcerative colitis and Crohn's disease are associated with an increased risk of dementia. But still this connection though being small underscores the importance of managing gut health to potentially reduce the risk of cognitive decline and Alzheimer's disease.

The higher percentage of respondents with no gut issues is beneficial, as gut health is probably linked to Alzheimer's disease risk. Chronic intestinal inflammation, such as seen in inflammatory bowel disease (IBD), can exacerbate AD pathology by promoting central nervous system inflammation and contributing to the formation of amyloid β-protein plaques and neurofibrillary tangles through the gut-brain axis (136).

II.3.3.Stress and Depression Levels of Respondents:

The majority of respondents reported moderate stress levels, which were higher compared to those with low or high stress levels. And those with depression were higher than without (Figure 32,33).

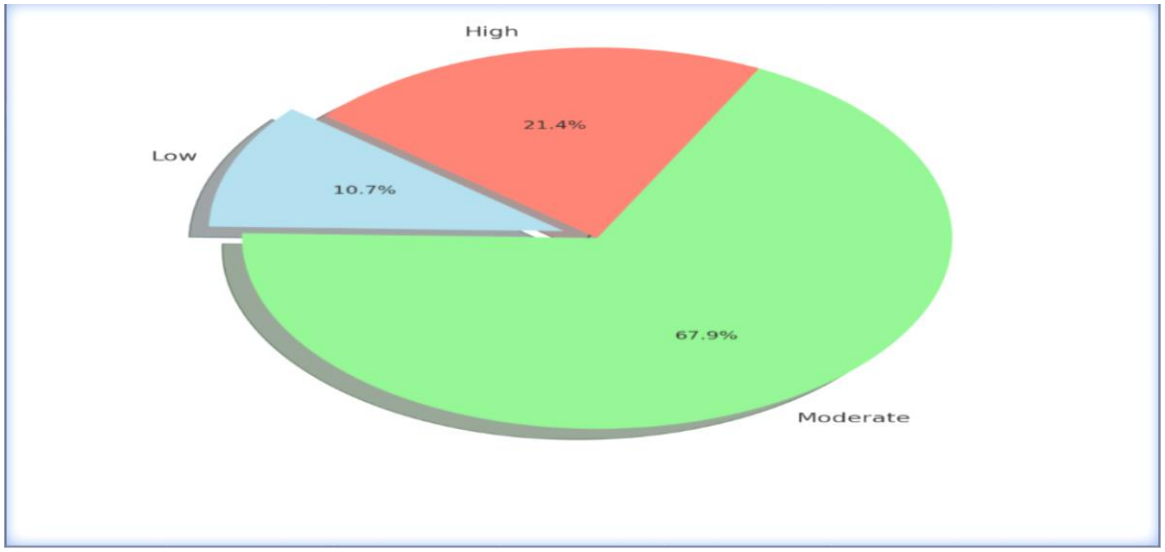

Figure 32 : Reported stress levels among the surveyed respondents.

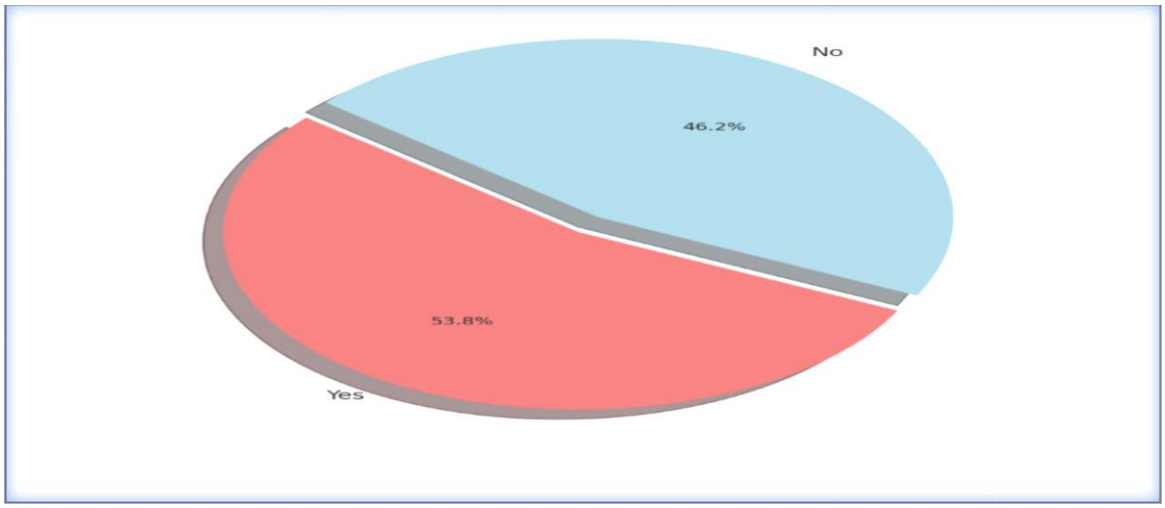

Figure 33 : Percentage of respondents with a history of depression.

The study of Jorm (2000), published a comprehensive literature review on the association between depression and Alzheimer's disease (AD). The studies reviewed present varying results, with relative risks ranging from 1.16 to 3.5 in case-control studies and 1.08 to 3.20 in cohort studies. The author highlights the challenge of interpreting this association, suggesting that the relationship between depression and AD remains complex and controversial (141).

The high percentage of respondents reporting depression (53.8%) is consistent with findings from Jorm's comprehensive review, which highlights the complex and potentially significant relationship between depression and Alzheimer's disease. This emphasizes the

importance of addressing mental health as a critical component in Alzheimer's disease prevention and management strategies. Further research is needed to clarify the nature of this association and develop effective interventions.

The majority of respondents reported moderate stress levels, and had depression, which may increase Alzheimer's disease risk. It is suggested that Stress accelerates amyloid pathology and tau phosphorylation in animal models, indicating a potential link to AD progression. Additionally, depression, commonly observed in AD patients, is both a consequence and potential risk factor for the disease. It is associated with lower CSF Aβ42, higher t-tau and p-tau levels, and atrophy in key brain regions, further exacerbating AD pathology (135).

II.3.Genetic factors:

II.3.1.Respondents with family members who had Alzheimer's disease:

A slightly higher percentage of respondents reported having no family members with Alzheimer's disease compared to those who did (Figure 34).

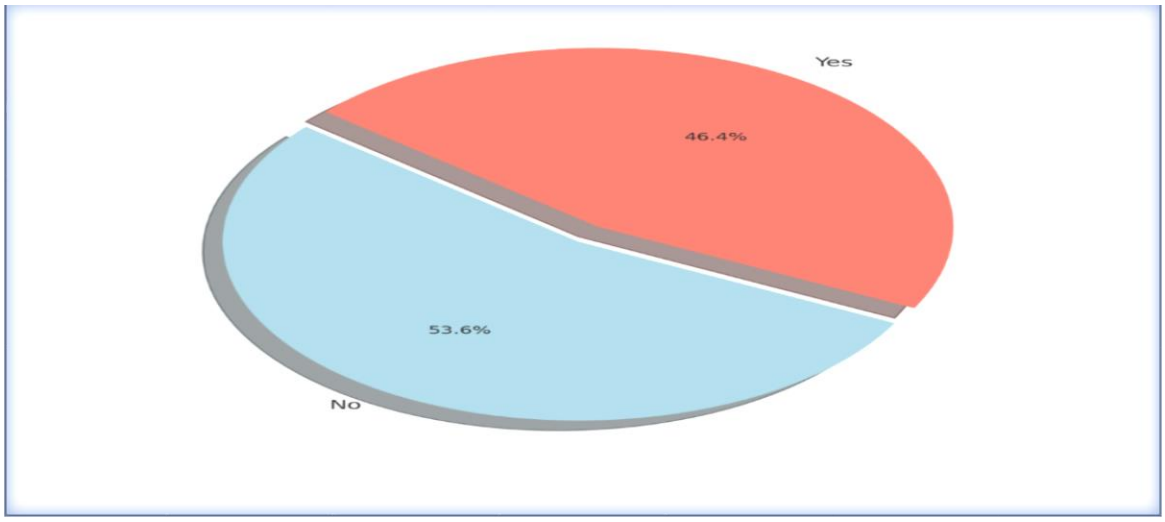

Figure 34 : Percentage of respondents with family members diagnosed with Alzheimer's disease.

An analysis of family history and Alzheimer's disease showed that individuals with a family history had a relative risk (RR) of 0.60 (95% CI: 0.13–2.66) for developing dementia. This suggests that, in this particular study, a family history of dementia did not significantly increase the risk (154).

In our study, 46.4% of respondents reported having family members with Alzheimer's disease, while 53.6% did not. Our findings indicate a higher proportion of individuals with a family history compared to the literature, suggesting that family history may still play a role in Alzheimer's risk within our population.

The majority of respondents reported having no family members with Alzheimer's disease, which may reduce their genetic risk. However, the 46.4% with affected family members face higher AD risk due to genetic factors. Mutations in APP, PSEN1, and PSEN2 genes drive early-onset AD by promoting amyloid aggregation, while the APOE ε4 allele increases late-onset AD risk by modulating immune responses, enhancing pro-inflammatory cytokine secretion, and impacting amyloid and tau pathology (119).

II.5.Oral health:

II.5.1.Respondents with gum problems (bleeding, pain, infections):

A higher percentage of respondents reported having no gum problems compared to those who did (Figure 35).

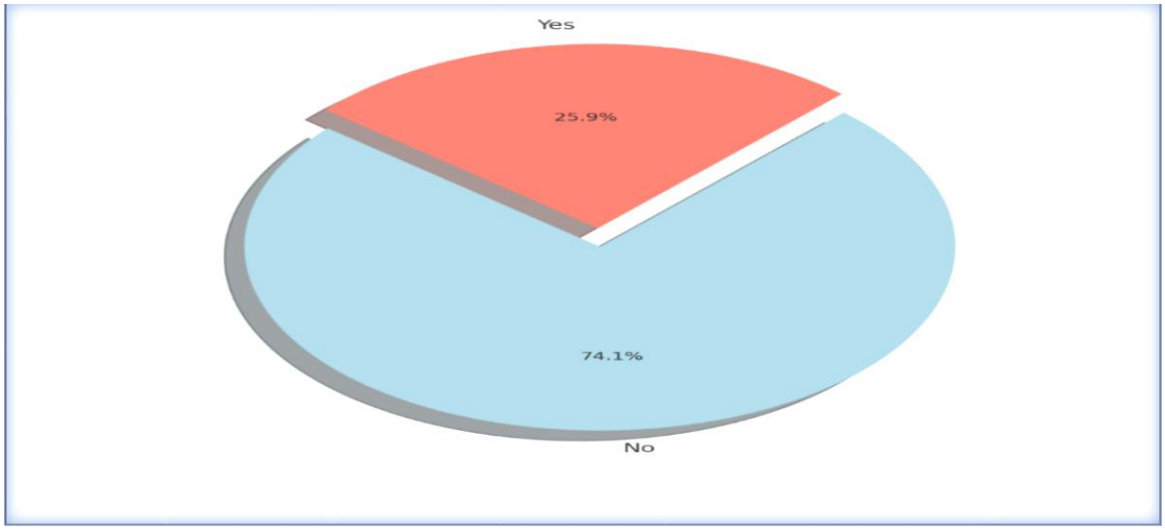

Figure 35 : Percentage of respondents reporting gum problems.

Studies have shown that patients with chronic periodontitis for at least eight years have a higher risk of developing cognitive decline and dementia. Oral health indicators such as gingival inflammation, attachment loss, probing depth, bleeding on probing, and alveolar bone loss are associated with cognitive impairment (155).

The survey results reveal that 74.1% of respondents consume fatty foods and lack healthy dietary habits, which contrasts sharply with the protective benefits of a Mediterranean diet highlighted in the New York study. This dietary pattern, rich in fruits, vegetables, whole grains, and healthy fats, is shown to significantly reduce the risk of Alzheimer's disease, emphasizing the need for dietary improvements to enhance cognitive health and reduce Alzheimer's risk in our population.

Oral health might contribute to Alzheimer's disease through mechanisms like gingipains and lipopolysaccharides from oral bacteria that activate glial cells, and inflammatory mediators crossing the blood-brain barrier via the olfactory and trigeminal nerves to cause neuroinflammation (137)

Conclusion and Perspective

Conclusion

The study examined various lifestyle factors influencing Alzheimer's disease (AD) progression through neuroinflammation in an Algerian population. The average age of respondents was 73.37 years, typical for Alzheimer's onset. A higher prevalence of dementia was found in women (72.4%), potentially due to hormonal changes after menopause.

Low education levels were reported by 35.7% of respondents, correlating with higher dementia risk from reduced cognitive reserves. Social engagement was high, with 89.7% being socially active, which generally helps protect against dementia.

Smoking was reported by 14.8% of respondents, increasing Alzheimer's risk through enhanced amyloid deposition and inflammation. No alcohol consumption was noted, suggesting a lower risk related to alcohol use.

Dietary habits were generally poor, potentially increasing Alzheimer's risk through gut microbiome disruptions and chronic inflammation, with 11.1% reporting gut issues. Chronic diseases were prevalent: 53.3% had hypertension, 20% diabetes, and 26.7% high cholesterol, all contributing to systemic inflammation.

Mental health issues included 53.8% of respondents reporting depression and moderate stress levels, both exacerbating Alzheimer's progression. Environmental exposure to neurotoxic chemicals like pesticides was reported by 11.1% of respondents.

Nearly half of the respondents (46.4%) had a family history of Alzheimer's, indicating a genetic predisposition. Poor oral health was common, contributing to Alzheimer's risk through inflammatory pathways initiated by oral bacteria. Good oral hygiene is crucial to reducing this risk.

To mitigate Alzheimer's disease risk, adopting a healthy lifestyle is crucial. Here are some recommendations:

- Stay socially active: Engage in social activities to maintain mental stimulation and support cognitive health.
- Avoid smoking and limit alcohol consumption: Smoking increases amyloid deposition and inflammation
- Maintain a balanced diet: Focus on a diet rich in fruits, vegetables, whole grains, and lean proteins to support gut health and reduce inflammation.
- Exercise Regularly: Physical activity improves cardiovascular health, reducing Alzheimer's risk.
- Monitor and manage chronic conditions: Keep conditions like hypertension, diabetes, and high cholesterol under control through regular check-ups and medication.
- Promote Mental Health: Address depression and stress through therapy, social support, and stress-reducing activities.
- Reduce exposure to neurotoxic chemicals: Minimize exposure to pesticides and other harmful chemicals.
- Take care of oral health: Maintain good oral hygiene to prevent inflammation related to poor oral health.
- Ensure good sleep quality: Prioritize sleep hygiene to support overall brain health.

Given these findings, adopting advanced diagnostic methods is essential for effectively managing Alzheimer's disease. In Algeria, using innovative techniques like retinal imaging and blood tests can greatly enhance early detection and management. Retinal imaging has shown that the retinas of newly diagnosed patients are significantly thinner due to amyloid plaque buildup. Emerging blood tests for early detection are also undergoing validation. Integrating these advanced methods can complement the recommended lifestyle changes to reduce risk.

Also based on our detailed investigation into the immunological mechanisms of Alzheimer's disease (AD), we propose that treatments should primarily target these aspects. Neuroinflammation significantly contributes to the progression of AD, with chronic immune cell activation intensifying neuronal damage. Therefore, therapies aimed at modulating the immune response, reducing inflammation, and preventing the infiltration of peripheral immune cells hold promise in slowing or halting disease progression. Addressing the immunological factors of AD could lead to more effective treatment options for patients.

These insights underscore the need for targeted interventions and public health strategies to address modifiable risk factors. Further research and tailored prevention and treatment strategies can significantly impact Alzheimer's disease prevalence and improve the quality of life for those at risk. Addressing these key areas can help better manage and potentially reduce the burden of Alzheimer's disease in Algeria and similar regions.

References

1. 2023 Alzheimer's disease facts and figures. Alzheimers Dement. 2023 Apr;19(4):1598–695.

2. El-Metwally A, Toivola P, Al-Rashidi M, Nooruddin S, Jawed M, AlKanhal R, et al. Epidemiology of Alzheimer's Disease and Dementia in Arab Countries: A Systematic Review. Behav Neurol. 2019 Oct 29;2019:1–14.

3. Hodges JR. Alzheimer's centennial legacy: origins, landmarks and the current status of knowledge concerning cognitive aspects. Brain. 2006 Sep 29;129(11):2811–22.

4. Otani K, Shichita T. Cerebral sterile inflammation in neurodegenerative diseases. Inflamm Regen. 2020 Dec;40(1):28.

5. Hammond TR, Marsh SE, Stevens B. Immune Signaling in Neurodegeneration. Immunity. 2019 Apr;50(4):955–74.

6. Villemagne VL, Burnham S, Bourgeat P, Brown B, Ellis KA, Salvado O, et al. Amyloid β deposition, neurodegeneration, and cognitive decline in sporadic Alzheimer's disease: a prospective cohort study. Lancet Neurol. 2013 Apr;12(4):357–67.

7. Jack CR, Wiste HJ, Lesnick TG, Weigand SD, Knopman DS, Vemuri P, et al. Brain β-amyloid load approaches a plateau. Neurology. 2013 Mar 5;80(10):890–6.

8. Pontecorvo MJ, Devous MD, Navitsky M, Lu M, Salloway S, Schaerf FW, et al. Relationships between flortaucipir PET tau binding and amyloid burden, clinical diagnosis, age and cognition. Brain. 2017 Jan 11;aww334.

9. Heneka MT, Kummer MP, Latz E. Innate immune activation in neurodegenerative disease. Nat Rev Immunol. 2014 Jul;14(7):463–77.

10. Korte N, Nortley R, Attwell D. Cerebral blood flow decrease as an early pathological mechanism in Alzheimer's disease. Acta Neuropathol (Berl). 2020 Dec;140(6):793–810.

11. Linnerbauer M, Wheeler MA, Quintana FJ. Astrocyte Crosstalk in CNS Inflammation. Neuron. 2020 Nov;108(4):608–22.

12. Onyango IG, Jauregui GV, Čarná M, Bennett JP, Stokin GB. Neuroinflammation in Alzheimer's Disease. Biomedicines. 2021 May 7;9(5):524.

13. Hansen DV, Hanson JE, Sheng M. Microglia in Alzheimer's disease. J Cell Biol. 2018 Feb 5;217(2):459–72.

14. Costantini E, D'Angelo C, Reale M. The Role of Immunosenescence in Neurodegenerative Diseases. Mediators Inflamm. 2018;2018:1–12.

15. Braak H, Braak E. Neuropathological stageing of Alzheimer-related changes. Acta Neuropathol (Berl). 1991 Sep;82(4):239–59.

16. Thal DR, Rüb U, Orantes M, Braak H. Phases of Aβ-deposition in the human brain and its relevance for the development of AD. Neurology. 2002 Jun 25;58(12):1791–800.

17. Terry RD, Masliah E, Salmon DP, Butters N, DeTeresa R, Hill R, et al. Physical basis of cognitive alterations in alzheimer's disease: Synapse loss is the major correlate of cognitive impairment. Ann Neurol. 1991 Oct;30(4):572–80.

18. Selkoe DJ. The molecular pathology of Alzheimer's disease. Neuron. 1991 Apr;6(4):487–98.

19. Kosik KS, Joachim CL, Selkoe DJ. Microtubule-associated protein tau (tau) is a major antigenic component of paired helical filaments in Alzheimer disease. Proc Natl Acad Sci. 1986 Jun;83(11):4044–8.

20. Jack CR, Petersen RC, Xu Y, O'Brien PC, Smith GE, Ivnik RJ, et al. Rate of medial temporal lobe atrophy in typical aging and Alzheimer's disease. Neurology. 1998 Oct;51(4):993–9.

21. Fox NC, Warrington EK, Freeborough PA, Hartikainen P, Kennedy AM, Stevens JM, et al. Presymptomatic hippocampal atrophy in Alzheimer's disease: A longitudinal MRI study. Brain. 1996;119(6):2001–7.

22. Greenberg SM, Bacskai BJ, Hernandez-Guillamon M, Pruzin J, Sperling R, Van Veluw SJ. Cerebral amyloid angiopathy and Alzheimer disease — one peptide, two pathways. Nat Rev Neurol. 2020 Jan;16(1):30–42.

23. Zlokovic BV. The Blood-Brain Barrier in Health and Chronic Neurodegenerative Disorders. Neuron. 2008 Jan;57(2):178–201.

24. Advanced Stages of Alzheimer's: Understanding the Stages - Altoida [Internet]. 2022 [cited 2024 Jul 1]. Available from: https://altoida.com/blog/advanced-stages-of-alzheimers-understanding-the-stages/

25. Dawkins E, Small DH. Insights into the physiological function of the β-amyloid precursor protein: beyond Alzheimer's disease. J Neurochem. 2014 Jun;129(5):756–69.

26. Moir RD, Lathe R, Tanzi RE. The antimicrobial protection hypothesis of Alzheimer's disease. Alzheimers Dement J Alzheimers Assoc. 2018 Dec;14(12):1602–14.

27. Eimer WA, Vijaya Kumar DK, Navalpur Shanmugam NK, Rodriguez AS, Mitchell T, Washicosky KJ, et al. Alzheimer's Disease-Associated β-Amyloid Is Rapidly Seeded by Herpesviridae to Protect against Brain Infection. Neuron. 2018 Jul 11;99(1):56-63.e3.

28. Giulian D, Haverkamp LJ, Yu J, Karshin W, Tom D, Li J, et al. The HHQK domain of beta-amyloid provides a structural basis for the immunopathology of Alzheimer's disease. J Biol Chem. 1998 Nov 6;273(45):29719–26.

29. Vukic V, Callaghan D, Walker D, Lue LF, Liu QY, Couraud PO, et al. Expression of inflammatory genes induced by beta-amyloid peptides in human brain endothelial cells and in Alzheimer's brain is mediated by the JNK-AP1 signaling pathway. Neurobiol Dis. 2009 Apr;34(1):95–106.

30. Sebollela A, Freitas-Correa L, Oliveira FF, Paula-Lima AC, Saraiva LM, Martins SM, et al. Amyloid-β oligomers induce differential gene expression in adult human brain slices. J Biol Chem. 2012 Mar 2;287(10):7436–45.

31. Reed-Geaghan EG, Savage JC, Hise AG, Landreth GE. CD14 and toll-like receptors 2 and 4 are required for fibrillar A{beta}-stimulated microglial activation. J Neurosci Off J Soc Neurosci. 2009 Sep 23;29(38):11982–92.

32. Landreth GE, Reed-Geaghan EG. Toll-like receptors in Alzheimer's disease. Curr Top Microbiol Immunol. 2009;336:137–53.

33. Bradt BM, Kolb WP, Cooper NR. Complement-dependent proinflammatory properties of the Alzheimer's disease beta-peptide. J Exp Med. 1998 Aug 3;188(3):431–8.

34. Bergamaschini L, Donarini C, Gobbo G, Parnetti L, Gallai V. Activation of complement and contact system in Alzheimer's disease. Mech Ageing Dev. 2001 Nov;122(16):1971–83.

35. Meraz-Rios M, Toral-Rios D, Franco-Bocanegra D, Villeda-Hernández J, Campos-Peña V. Inflammatory Process in Alzheimer's Disease. Front Integr Neurosci. 2013 Aug 13;7:59.

36. Heneka MT, Carson MJ, El Khoury J, Landreth GE, Brosseron F, Feinstein DL, et al. Neuroinflammation in Alzheimer's disease. Lancet Neurol. 2015 Apr;14(4):388–405.

37. Heppner FL, Ransohoff RM, Becher B. Immune attack: the role of inflammation in Alzheimer disease. Nat Rev Neurosci. 2015 Jun;16(6):358–72.

38. Popp J, Oikonomidi A, Tautvydaitė D, Dayon L, Bacher M, Migliavacca E, et al. Markers of neuroinflammation associated with Alzheimer's disease pathology in older adults. Brain Behav Immun. 2017 May;62:203–11.

39. Laurent C, Buée L, Blum D. Tau and neuroinflammation: What impact for Alzheimer's Disease and Tauopathies? Biomed J. 2018 Feb;41(1):21–33.

40. Itzhaki RF, Lathe R, Balin BJ, Ball MJ, Bearer EL, Braak H, et al. Microbes and Alzheimer's Disease. J Alzheimers Dis JAD. 2016;51(4):979–84.

41. Varnum MM, Ikezu T. The classification of microglial activation phenotypes on neurodegeneration and regeneration in Alzheimer's disease brain. Arch Immunol Ther Exp (Warsz). 2012 Aug;60(4):251–66.

42. Busciglio J, Pelsman A, Wong C, Pigino G, Yuan M, Mori H, et al. Altered metabolism of the amyloid beta precursor protein is associated with mitochondrial dysfunction in Down's syndrome. Neuron. 2002 Feb 28;33(5):677–88.

43. Outreach R. Disruption of amyloid β-protein processing drives Alzheimer's [Internet]. Research Outreach. 2021 [cited 2024 May 23]. Available from: https://researchoutreach.org/articles/disruption-amyloid-β-protein-processing-drives-alzheimers/

44. Guo JT, Yu J, Grass D, de Beer FC, Kindy MS. Inflammation-dependent cerebral deposition of serum amyloid a protein in a mouse model of amyloidosis. J Neurosci Off J Soc Neurosci. 2002 Jul 15;22(14):5900–9.

45. Sastre M, Dewachter I, Landreth GE, Willson TM, Klockgether T, van Leuven F, et al. Nonsteroidal anti-inflammatory drugs and peroxisome proliferator-activated receptor-gamma agonists modulate immunostimulated processing of amyloid precursor protein through regulation of beta-secretase. J Neurosci Off J Soc Neurosci. 2003 Oct 29;23(30):9796–804.

46. Sastre M, Klockgether T, Heneka MT. Contribution of inflammatory processes to Alzheimer's disease: molecular mechanisms. Int J Dev Neurosci Off J Int Soc Dev Neurosci. 2006;24(2–3):167–76.

47. Chen CH, Zhou W, Liu S, Deng Y, Cai F, Tone M, et al. Increased NF-κB signalling up-regulates BACE1 expression and its therapeutic potential in Alzheimer's disease. Int J Neuropsychopharmacol. 2012 Feb;15(1):77–90.

48. Zhang W, Xiao D, Mao Q, Xia H. Role of neuroinflammation in neurodegeneration development. Signal Transduct Target Ther. 2023 Jul 12;8:267.

49. Llano DA, Li J, Waring JF, Ellis T, Devanarayan V, Witte DG, et al. Cerebrospinal fluid cytokine dynamics differ between Alzheimer disease patients and elderly controls. Alzheimer Dis Assoc Disord. 2012;26(4):322–8.

50. Rosén C, Andersson CH, Andreasson U, Molinuevo JL, Bjerke M, Rami L, et al. Increased Levels of Chitotriosidase and YKL-40 in Cerebrospinal Fluid from Patients with Alzheimer's Disease. Dement Geriatr Cogn Disord Extra. 2014 Jul 31;4(2):297–304.

51. Streit WJ, Mrak RE, Griffin WST. Microglia and neuroinflammation: a pathological perspective. J Neuroinflammation. 2004 Jul 30;1(1):14.

52. Liu B, Hong JS. Role of microglia in inflammation-mediated neurodegenerative diseases: mechanisms and strategies for therapeutic intervention. J Pharmacol Exp Ther. 2003 Jan;304(1):1–7.

53. Barger SW, Harmon AD. Microglial activation by Alzheimer amyloid precursor protein and modulation by apolipoprotein E. Nature. 1997 Aug 28;388(6645):878–81.

54. Ho GJ, Drego R, Hakimian E, Masliah E. Mechanisms of cell signaling and inflammation in Alzheimer's disease. Curr Drug Targets Inflamm Allergy. 2005 Apr;4(2):247–56.

55. Akiyama H, Barger S, Barnum S, Bradt B, Bauer J, Cole GM, et al. Inflammation and Alzheimer's disease. Neurobiol Aging. 2000;21(3):383–421.

56. Schilling T, Eder C. Amyloid-β-induced reactive oxygen species production and priming are differentially regulated by ion channels in microglia. J Cell Physiol. 2011 Dec;226(12):3295–302.

57. Long HZ, Zhou ZW, Cheng Y, Luo HY, Li FJ, Xu SG, et al. The Role of Microglia in Alzheimer's Disease From the Perspective of Immune Inflammation and Iron Metabolism.

Front Aging Neurosci [Internet]. 2022 Jun 30 [cited 2024 May 13];14. Available from: https://www.frontiersin.org/articles/10.3389/fnagi.2022.888989

58. Morales I, Guzmán-Martínez L, Cerda-Troncoso C, Farías GA, Maccioni RB. Neuroinflammation in the pathogenesis of Alzheimer's disease. A rational framework for the search of novel therapeutic approaches. Front Cell Neurosci. 2014;8:112.

59. Phillips EC, Croft CL, Kurbatskaya K, O'Neill MJ, Hutton ML, Hanger DP, et al. Astrocytes and neuroinflammation in Alzheimer's disease. Biochem Soc Trans. 2014 Oct;42(5):1321–5.

60. Reid JK, Kuipers HF. She Doesn't Even Go Here: The Role of Inflammatory Astrocytes in CNS Disorders. Front Cell Neurosci [Internet]. 2021 Sep 3 [cited 2024 May 13];15. Available from: https://www.frontiersin.org/articles/10.3389/fncel.2021.704884

61. Herpes simplex virus type 1 and Alzheimer's disease: increasing evidence for a major role of the virus - PMC [Internet]. [cited 2024 May 14]. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4128394/

62. Ciccocioppo F, Lanuti P, Pierdomenico L, Simeone P, Bologna G, Ercolino E, et al. The Characterization of Regulatory T-Cell Profiles in Alzheimer's Disease and Multiple Sclerosis. Sci Rep. 2019 Jun 19;9(1):8788.

63. Louveau A, Harris TH, Kipnis J. Revisiting the Mechanisms of CNS Immune Privilege. Trends Immunol. 2015 Oct;36(10):569–77.

64. Louveau A, Smirnov I, Keyes TJ, Eccles JD, Rouhani SJ, Peske JD, et al. Structural and functional features of central nervous system lymphatic vessels. Nature. 2015 Jul 16;523(7560):337–41.

65. Ahn JH, Cho H, Kim JH, Kim SH, Ham JS, Park I, et al. Meningeal lymphatic vessels at the skull base drain cerebrospinal fluid. Nature. 2019 Aug;572(7767):62–6.

66. Absinta M, Ha SK, Nair G, Sati P, Luciano NJ, Palisoc M, et al. Human and nonhuman primate meninges harbor lymphatic vessels that can be visualized noninvasively by MRI. eLife. 2017 Oct 3;6:e29738.

67. Acharya NK, Nagele EP, Han M, Coretti NJ, DeMarshall C, Kosciuk MC, et al. Neuronal PAD4 expression and protein citrullination: possible role in production of autoantibodies associated with neurodegenerative disease. J Autoimmun. 2012 Jun;38(4):369–80.

68. Louveau A, Herz J, Alme MN, Salvador AF, Dong MQ, Viar KE, et al. CNS lymphatic drainage and neuroinflammation are regulated by meningeal lymphatic vasculature. Nat Neurosci. 2018 Oct;21(10):1380–91.

69. Schwartz N, Chalasani MLS, Li TM, Feng Z, Shipman WD, Lu TT. Lymphatic Function in Autoimmune Diseases. Front Immunol. 2019;10:519.

70. Da Mesquita S, Louveau A, Vaccari A, Smirnov I, Cornelison RC, Kingsmore KM, et al. Functional aspects of meningeal lymphatics in ageing and Alzheimer's disease. Nature. 2018 Aug;560(7717):185–91.

71. Berer K, Mues M, Koutrolos M, Rasbi ZA, Boziki M, Johner C, et al. Commensal microbiota and myelin autoantigen cooperate to trigger autoimmune demyelination. Nature. 2011 Nov;479(7374):538–41.

72. Sampson TR, Debelius JW, Thron T, Janssen S, Shastri GG, Ilhan ZE, et al. Gut Microbiota Regulate Motor Deficits and Neuroinflammation in a Model of Parkinson's Disease. Cell. 2016 Dec 1;167(6):1469-1480.e12.

73. Minter MR, Zhang C, Leone V, Ringus DL, Zhang X, Oyler-Castrillo P, et al. Antibiotic-induced perturbations in gut microbial diversity influences neuro-inflammation and amyloidosis in a murine model of Alzheimer's disease. Sci Rep. 2016 Jul 21;6(1):30028.

74. Bairamian D, Sha S, Rolhion N, Sokol H, Dorothée G, Lemere CA, et al. Microbiota in neuroinflammation and synaptic dysfunction: a focus on Alzheimer's disease. Mol Neurodegener. 2022 Mar 5;17(1):19.

75. Vogt NM, Kerby RL, Dill-McFarland KA, Harding SJ, Merluzzi AP, Johnson SC, et al. Gut microbiome alterations in Alzheimer's disease. Sci Rep. 2017 Oct 19;7(1):13537.

76. Harach T, Marungruang N, Duthilleul N, Cheatham V, Mc Coy KD, Frisoni G, et al. Reduction of Abeta amyloid pathology in APPPS1 transgenic mice in the absence of gut microbiota. Sci Rep. 2017 Feb 8;7(1):41802.

77. Mezö C, Dokalis N, Mossad O, Staszewski O, Neuber J, Yilmaz B, et al. Different effects of constitutive and induced microbiota modulation on microglia in a mouse model of Alzheimer's disease. Acta Neuropathol Commun. 2020 Jul 29;8(1):119.

78. Cattaneo A, Cattane N, Galluzzi S, Provasi S, Lopizzo N, Festari C, et al. Association of brain amyloidosis with pro-inflammatory gut bacterial taxa and peripheral inflammation markers in cognitively impaired elderly. Neurobiol Aging. 2017 Jan 1;49:60–8.

79. Bonaz B, Bazin T, Pellissier S. The Vagus Nerve at the Interface of the Microbiota-Gut-Brain Axis. Front Neurosci [Internet]. 2018 Feb 7 [cited 2024 May 20];12. Available from: https://www.frontiersin.org/journals/neuroscience/articles/10.3389/fnins.2018.00049/full

80. Bravo JA, Forsythe P, Chew MV, Escaravage E, Savignac HM, Dinan TG, et al. Ingestion of Lactobacillus strain regulates emotional behavior and central GABA receptor expression in a mouse via the vagus nerve. Proc Natl Acad Sci. 2011 Sep 20;108(38):16050–5.

81. Focusing on the gut-brain axis: new opportunities on the horizon for treating Alzheimer and other neurodegenerative diseases [Internet]. [cited 2024 May 20]. Available from: https://synapse.patsnap.com/blog/focusing-on-the-gut-brain-axis-new-opportunities-on-the-horizon-for-treating-alzheimer-and-other-neurodegenerative-diseases

82. Carreno G, Guiho R, Martinez-Barbera JP. Cell senescence in neuropathology: A focus on neurodegeneration and tumours. Neuropathol Appl Neurobiol. 2021 Apr;47(3):359–78.

83. Ratushnyy AY, Rudimova YV, Buravkova LB. Replicative Senescence and Expression of Autophagy Genes in Mesenchymal Stromal Cells. Biochem Mosc. 2020 Oct;85(10):1169–77.

84. López-Olóriz J, López-Cancio E, Arenillas JF, Hernández M, Jiménez M, Dorado L, et al. Asymptomatic cervicocerebral atherosclerosis, intracranial vascular resistance and cognition: The AsIA-Neuropsychology Study. Atherosclerosis. 2013 Oct;230(2):330–5.

85. Franceschi C, Bonafè M, Valensin S, Olivieri F, De Luca M, Ottaviani E, et al. Inflamm-aging: An Evolutionary Perspective on Immunosenescence. Ann N Y Acad Sci. 2000 Jun;908(1):244–54.

86. Mijit M, Caracciolo V, Melillo A, Amicarelli F, Giordano A. Role of p53 in the Regulation of Cellular Senescence. Biomolecules. 2020 Mar 8;10(3):420.

87. Walton CC, Begelman D, Nguyen W, Andersen JK. Senescence as an Amyloid Cascade: The Amyloid Senescence Hypothesis. Front Cell Neurosci [Internet]. 2020 May 19 [cited 2024 May 23];14. Available from: https://www.frontiersin.org/articles/10.3389/fncel.2020.00129

88. Farrer LA. Effects of Age, Sex, and Ethnicity on the Association Between Apolipoprotein E Genotype and Alzheimer Disease: A Meta-analysis. JAMA. 1997 Oct 22;278(16):1349.

89. Jett S, Schelbaum E, Jang G, Boneu Yepez C, Dyke JP, Pahlajani S, et al. Ovarian steroid hormones: A long overlooked but critical contributor to brain aging and Alzheimer's disease. Front Aging Neurosci. 2022 Jul 19;14:948219.

90. Wang Y, Mishra A, Brinton RD. Transitions in metabolic and immune systems from pre-menopause to post-menopause: implications for age-associated neurodegenerative diseases. F1000Research. 2020 Jan 30;9:68.

91. Aslam F. Obesity and CRP. Ann Rheum Dis. 2017 Oct 4;annrheumdis-2017-212425.

92. Mavri A, Alessi MC, Geel-Georgelin O, Fina F, Sentocnik JT, Bastelica D, et al. Subcutaneous abdominal, but not femoral fat expression of plasminogen activator inhibitor-1 (PAI-1) is related to plasma PAI-1 levels and insulin resistance and decreases after weight loss. Diabetologia. 2001 Nov 1;44(11):2025–31.

93. Marques-Vidal P, Bochud M, Bastardot F, Lüscher T, Ferrero F, Gaspoz JM, et al. Association between Inflammatory and Obesity Markers in a Swiss Population-Based Sample (CoLaus Study). Obes Facts. 2012;5(5):734–44.

94. Den Hartigh LJ, Wang S, Goodspeed L, Ding Y, Averill M, Subramanian S, et al. Deletion of Serum Amyloid A3 Improves High Fat High Sucrose Diet-Induced Adipose Tissue Inflammation and Hyperlipidemia in Female Mice. Wong GW, editor. PLoS ONE. 2014 Sep 24;9(9):e108564.

95. Piché ME, Tchernof A, Després JP. Obesity Phenotypes, Diabetes, and Cardiovascular Diseases. Circ Res. 2020 May 22;126(11):1477–500.

96. Durazzo TC, Mattsson N, Weiner MW. Smoking and increased Alzheimer's disease risk: A review of potential mechanisms. Alzheimers Dement J Alzheimers Assoc. 2014 Jun;10(3 0):S122–45.

97. Andrews SJ, Goate A, Anstey KJ. Association between alcohol consumption and Alzheimer's disease: A Mendelian randomization study. Alzheimers Dement. 2020;16(2):345–53.

98. Akhter-Khan SC, Tao Q, Ang TFA, Itchapurapu IS, Alosco ML, Mez J, et al. Associations of loneliness with risk of Alzheimer's disease dementia in the Framingham Heart Study. Alzheimers Dement J Alzheimers Assoc. 2021 Oct;17(10):1619–27.

99. Minakawa EN, Wada K, Nagai Y. Sleep Disturbance as a Potential Modifiable Risk Factor for Alzheimer's Disease. Int J Mol Sci. 2019 Feb 13;20(4):803.

100. Elonheimo HM, Andersen HR, Katsonouri A, Tolonen H. Environmental Substances Associated with Alzheimer's Disease—A Scoping Review. Int J Environ Res Public Health. 2021 Nov 11;18(22):11839.

101. Statovci D, Aguilera M, MacSharry J, Melgar S. The Impact of Western Diet and Nutrients on the Microbiota and Immune Response at Mucosal Interfaces. Front Immunol. 2017 Jul 28;8:838.

102. Christ A, Lauterbach M, Latz E. Western Diet and the Immune System: An Inflammatory Connection. Immunity. 2019 Nov;51(5):794–811.

103. Requena T, Martínez-Cuesta MC, Peláez C. Diet and microbiota linked in health and disease. Food Funct. 2018;9(2):688–704.

104. De Roos A, Van Der Grond J, Mitchell G, Westenberg J. Magnetic Resonance Imaging of Cardiovascular Function and the Brain: Is Dementia a Cardiovascular-Driven Disease? Circulation. 2017 May 30;135(22):2178–95.

105. Pelkman CL. Effects of the glycemic index of foods on serum concentrations of high-density lipoprotein cholesterol and triglycerides. Curr Atheroscler Rep. 2001 Nov;3(6):456–61.

106. Raits E, Kirse-Ozolina A. Modern dietary patterns based on territorial origin - a review. In 2019. p. 19–24.

107. Scarmeas N, Stern Y, Mayeux R, Manly JJ, Schupf N, Luchsinger JA. Mediterranean Diet and Mild Cognitive Impairment. Arch Neurol [Internet]. 2009 Feb 1 [cited 2024 May 20];66(2). Available from: http://archneur.jamanetwork.com/article.aspx?doi=10.1001/archneurol.2008.536

108. Van De Rest O, Berendsen AA, Haveman-Nies A, De Groot LC. Dietary Patterns, Cognitive Decline, and Dementia: A Systematic Review. Adv Nutr. 2015 Mar;6(2):154–68.

109. Samieri C, Okereke OI, E. Devore E, Grodstein F. Long-Term Adherence to the Mediterranean Diet Is Associated with Overall Cognitive Status, but Not Cognitive Decline, in Women. J Nutr. 2013 Apr;143(4):493–9.

110. Anastasiou CA, Yannakoulia M, Kosmidis MH, Dardiotis E, Hadjigeorgiou GM, Sakka P, et al. Mediterranean diet and cognitive health: Initial results from the Hellenic Longitudinal Investigation of Ageing and Diet. Feart C, editor. PLOS ONE. 2017 Aug 1;12(8):e0182048.

111. Loughrey DG, Lavecchia S, Brennan S, Lawlor BA, Kelly ME. The Impact of the Mediterranean Diet on the Cognitive Functioning of Healthy Older Adults: A Systematic Review and Meta-Analysis. Adv Nutr. 2017 Jul;8(4):571–86.

112. Scarmeas N, Stern Y, Tang M, Mayeux R, Luchsinger JA. Mediterranean diet and risk for Alzheimer's disease. Ann Neurol. 2006 Jun;59(6):912–21.

113. RecipeTips.com [Internet]. [cited 2024 May 23]. Mediterranean Diet Pyramid. Available from: https://www.recipetips.com/glossary-term/t--38810/mediterranean-diet-pyramid.asp

114. Zhang Q, Sidorenko J, Couvy-Duchesne B, Marioni RE, Wright MJ, Goate AM, et al. Risk prediction of late-onset Alzheimer's disease implies an oligogenic architecture. Nat Commun. 2020 Sep 23;11(1):4799.

115. Hashioka S, Inoue K, Takeshita H, Inagaki M. Do Alzheimer's Disease Risk Gene Products Actually Act in Microglia? Front Aging Neurosci. 2020 Dec 3;12:589196.

116. Lynch JR, Pineda JA, Morgan D, Zhang L, Warner DS, Benveniste H, et al. Apolipoprotein E affects the central nervous system response to injury and the development of cerebral edema. Ann Neurol. 2002 Jan;51(1):113–7.

117. Kang SS, Ebbert MTW, Baker KE, Cook C, Wang X, Sens JP, et al. Microglial translational profiling reveals a convergent APOE pathway from aging, amyloid, and tau. J Exp Med. 2018 Sep 3;215(9):2235–45.

118. Troutwine BR, Hamid L, Lysaker CR, Strope TA, Wilkins HM. Apolipoprotein E and Alzheimer's disease. Acta Pharm Sin B. 2022 Feb 1;12(2):496–510.

119. Yamazaki Y, Zhao N, Caulfield TR, Liu CC, Bu G. Apolipoprotein E and Alzheimer disease: pathobiology and targeting strategies. Nat Rev Neurol. 2019 Sep;15(9):501–18.

120. Rebeck GW. The role of APOE on lipid homeostasis and inflammation in normal brains. J Lipid Res. 2017 Aug;58(8):1493–9.

121. Zhao N, Liu CC, Van Ingelgom AJ, Martens YA, Linares C, Knight JA, et al. Apolipoprotein E4 Impairs Neuronal Insulin Signaling by Trapping Insulin Receptor in the Endosomes. Neuron. 2017 Sep;96(1):115-129.e5.

122. Krasemann S, Madore C, Cialic R, Baufeld C, Calcagno N, El Fatimy R, et al. The TREM2-APOE Pathway Drives the Transcriptional Phenotype of Dysfunctional Microglia in Neurodegenerative Diseases. Immunity. 2017 Sep;47(3):566-581.e9.

123. Atagi Y, Liu CC, Painter MM, Chen XF, Verbeeck C, Zheng H, et al. Apolipoprotein E Is a Ligand for Triggering Receptor Expressed on Myeloid Cells 2 (TREM2). J Biol Chem. 2015 Oct;290(43):26043–50.

124. Roher AE, Tyas SL, Maarouf CL, Daugs ID, Kokjohn TA, Emmerling MR, et al. Intracranial atherosclerosis as a contributing factor to Alzheimer's disease dementia. Alzheimers Dement. 2011 Jul;7(4):436–44.

125. Paffen E, Demaat M. C-reactive protein in atherosclerosis: A causal factor? Cardiovasc Res. 2006 Jul 1;71(1):30–9.

126. Heneka MT, Kummer MP, Stutz A, Delekate A, Schwartz S, Vieira-Saecker A, et al. NLRP3 is activated in Alzheimer's disease and contributes to pathology in APP/PS1 mice. Nature. 2013 Jan;493(7434):674–8.

127. Guo H, Callaway JB, Ting JPY. Inflammasomes: mechanism of action, role in disease, and therapeutics. Nat Med. 2015 Jul;21(7):677–87.

128. Arvanitakis Z, Wilson RS, Bienias JL, Evans DA, Bennett DA. Diabetes Mellitus and Risk of Alzheimer Disease and Decline in Cognitive Function. Arch Neurol. 2004 May 1;61(5):661.

129. Pugazhenthi S, Qin L, Reddy PH. Common neurodegenerative pathways in obesity, diabetes, and Alzheimer's disease. Biochim Biophys Acta BBA - Mol Basis Dis. 2017 May;1863(5):1037–45.

130. Arancio O, Zhang HP, Chen X, Lin C, Trinchese F, Puzzo D, et al. RAGE potentiates Aβ-induced perturbation of neuronal function in transgenic mice. EMBO J. 2004 Oct 13;23(20):4096–105.

131. Choi BR, Cho WH, Kim J, Lee HJ, Chung C, Jeon WK, et al. Increased expression of the receptor for advanced glycation end products in neurons and astrocytes in a triple transgenic mouse model of Alzheimer's disease. Exp Mol Med. 2014 Feb 7;46(2):e75–e75.

132. Cook DG, Leverenz JB, McMillan PJ, Kulstad JJ, Ericksen S, Roth RA, et al. Reduced Hippocampal Insulin-Degrading Enzyme in Late-Onset Alzheimer's Disease Is Associated with the Apolipoprotein E-ε4 Allele. Am J Pathol. 2003 Jan;162(1):313–9.

133. Nazareth A. Type 2 diabetes mellitus in the pathophysiology of Alzheimer's disease. Dement E Neuropsychol. 2017 Jun 1;11:105–13.

134. Botto R, Callai N, Cermelli A, Causarano L, Rainero I. Anxiety and depression in Alzheimer's disease: a systematic review of pathogenetic mechanisms and relation to cognitive decline. Neurol Sci. 2022;43(7):4107–24.

135. Mohammadi S, Zandi M, Dousti Kataj P, Karimi Zandi L. Chronic stress and Alzheimer's disease. Biotechnol Appl Biochem. 2022 Aug;69(4):1451–8.

136. Wang D, Zhang X, Du H. Inflammatory bowel disease: A potential pathogenic factor of Alzheimer's disease. Prog Neuropsychopharmacol Biol Psychiatry. 2022 Dec 20;119:110610.

137. Zhang M, Mi N, Ying Z, Lin X, Jin Y. Advances in the prevention and treatment of Alzheimer's disease based on oral bacteria. Front Psychiatry. 2023 Dec 13;14:1291455.

138. Diagnostic de la maladie d'Alzheimer [Internet]. Fondation Recherche Alzheimer. [cited 2024 Jun 10]. Available from: https://alzheimer-recherche.org/la-maladie-alzheimer/symptomes-et-diagnostic/diagnostic/

139. Bellio M. Translating Predictive Models for Alzheimer's Disease to Clinical Practice: User Research, Adoption Opportunities, and Conceptual Design of a Decision Support Tool. In 2021.

140. Stocker H, Trares K, Beyer L, Perna L, Rujescu D, Holleczek B, et al. Alzheimer's polygenic risk scores, APOE, Alzheimer's disease risk, and dementia-related blood biomarker levels in a population-based cohort study followed over 17 years. Alzheimers Res Ther. 2023 Jul 29;15(1):129.

141. GBD 2019 Dementia Forecasting Collaborators. Estimation of the global prevalence of dementia in 2019 and forecasted prevalence in 2050: an analysis for the Global Burden of Disease Study 2019. Lancet Public Health. 2022 Feb;7(2):e105–25.

142. Livingston G, Huntley J, Sommerlad A, Ames D, Ballard C, Banerjee S, et al. Dementia prevention, intervention, and care: 2020 report of the Lancet Commission. Lancet Lond Engl. 2020;396(10248):413–46.

143. Arango C, Dragioti E, Solmi M, Cortese S, Domschke K, Murray RM, et al. Risk and protective factors for mental disorders beyond genetics: an evidence-based atlas. World Psychiatry. 2021 Oct;20(3):417–36.

144. Anstey KJ, von Sanden C, Salim A, O'Kearney R. Smoking as a risk factor for dementia and cognitive decline: a meta-analysis of prospective studies. Am J Epidemiol. 2007 Aug 15;166(4):367–78.

145. Schwarzinger M, Pollock BG, Hasan OSM, Dufouil C, Rehm J, QalyDays Study Group. Contribution of alcohol use disorders to the burden of dementia in France 2008-13: a nationwide retrospective cohort study. Lancet Public Health. 2018 Mar;3(3):e124–32.

146. Yan D, Zhang Y, Liu L, Yan H. Pesticide exposure and risk of Alzheimer's disease: a systematic review and meta-analysis. Sci Rep. 2016 Sep 1;6:32222.

147. Anderson EL, Richmond RC, Jones SE, Hemani G, Wade KH, Dashti HS, et al. Is disrupted sleep a risk factor for Alzheimer's disease? Evidence from a two-sample Mendelian randomization analysis. Int J Epidemiol. 2021 Jul 9;50(3):817–28.

148. Xu W, Tan L, Wang HF, Jiang T, Tan MS, Tan L, et al. Meta-analysis of modifiable risk factors for Alzheimer's disease. J Neurol Neurosurg Psychiatry. 2015 Dec;86(12):1299–306.

149. Pedditzi E, Peters R, Beckett N. The risk of overweight/obesity in mid-life and late life for the development of dementia: a systematic review and meta-analysis of longitudinal studies. Age Ageing. 2016 Jan;45(1):14–21.

150. McGrath ER, Beiser AS, DeCarli C, Plourde KL, Vasan RS, Greenberg SM, et al. Blood pressure from mid- to late life and risk of incident dementia. Neurology. 2017 Dec 12;89(24):2447–54.

151. Chatterjee S, Peters SAE, Woodward M, Mejia Arango S, Batty GD, Beckett N, et al. Type 2 Diabetes as a Risk Factor for Dementia in Women Compared With Men: A Pooled Analysis of 2.3 Million People Comprising More Than 100,000 Cases of Dementia. Diabetes Care. 2016 Feb;39(2):300–7.

152. Global burden of 87 risk factors in 204 countries and territories, 1990–2019: a systematic analysis for the Global Burden of Disease Study 2019. Lancet Lond Engl. 2020 Oct 17;396(10258):1223–49.

153. Rønnow Sand J, Troelsen FS, Horváth-Puhó E, Henderson VW, Sørensen HT, Erichsen R. Risk of dementia in patients with inflammatory bowel disease: a Danish population-based study. Aliment Pharmacol Ther. 2022 Sep;56(5):831–43.

154. Tyas SL, Manfreda J, Strain LA, Montgomery PR. Risk factors for Alzheimer's disease: a population-based, longitudinal study in Manitoba, Canada. Int J Epidemiol. 2001 Jun 1;30(3):590–7.

155. Said-Sadier N, Sayegh B, Farah R, Abbas LA, Dweik R, Tang N, et al. Association between Periodontal Disease and Cognitive Impairment in Adults. Int J Environ Res Public Health. 2023 Mar 7;20(6):4707.

2023-2024	**Presented by: Saci Nada**

Risk Factors for Alzheimer's Disease: An immunopathogenesis perspective

This study investigates various risk factors for Alzheimer's disease (AD) through a comprehensive survey of 29 patients and statistical analysis using SPSS. Given the small sample size, these results should be interpreted with caution and cannot be solely relied upon for definitive conclusions.

Our analysis confirmed that age and sex significantly influence AD prevalence, with older adults and females being more affected. Midlife obesity, lower educational attainment, family history of AD, smoking, depression, and chronic stress were identified as significant risk factors. Conversely, moderate alcohol consumption and social engagement appeared to reduce the risk of AD.

The study also highlighted the importance of oral health, as chronic gum problems were associated with higher dementia risk. Poor sleep quality and exposure to neurotoxic chemicals, particularly pesticides, were linked to increased AD risk. Furthermore, diet and gut health were crucial, with unhealthy diets and inflammatory bowel disease (IBD) contributing to higher dementia prevalence.

Additionally, the literature review provided an in-depth explanation of the immunopathogenesis hypotheses of AD causes, which is a crucial part of understanding the disease mechanisms. Overall, the findings reinforce the multifactorial nature of Alzheimer's disease and the need for a holistic approach to its prevention and management. Future research should focus on these associations to develop targeted interventions.

Key words: Alzheimer’s disease,Neuroinflammation,Risk factors

Présidente du jury : ZERIZER sakina (**Pr.**Université des Frères Mentouri,Constantine 1).

Encadreur : AGGOUN cherifa (**MCB.**Université des Frères Mentouri,Constantine 1).

Examinatrice : HADDAD souad **(MAA.**Université des Frères Mentouri,Constantine 1).