A quantitative study: How inflammatory diet affects different neurotransmitters' function and their relation to memory disorders.

Abdelrahman Gamal (Ismailia STEM high school)
Adam Hassan (Fayoum STEM high school)
Karim Morgan (Gharbiya STEM high school)
Mentor: Habiba Sorour

Abstract

Alzheimer's disease has been a case study for a long time, discoveries brought hypotheses and reasons related to the disease mechanism. This study aims to bring a clear understanding of the significant impact of human actions such as diet and Alzheimer's disease. Diet indirectly impacts the human body and significantly the brain, in the case of memory disorder diet affects the neurotransmitters that play an important role in the function of the brain and memory. The study used various relations between variables, hypotheses show that a transmembrane protein plays a key role in neurodegeneration and later it disturbs the neurotransmitter's function. Through the study, information showed that diet styles cause oxidative stress which is considered one of the main reasons that cause neurodegeneration. The study shows the impact of each variable on the other and leads these findings to the main case study of Alzheimer's disease.

I. Introduction

The brain is an Extortionary organ as it is responsible for thoughts, memories, and movement of the body systems and function, furthermore, the brain health acquires attention and care. Due to the brain's vulnerability to some disorders. cognitive brain disorders occur due to the detectable destruction of brain connections or networks between neurons, and neurodegenerative diseases such as Alzheimer's disease (AD), Parkinson's Disease (PD), Schizophrenia, Depression, and Multiple Sclerosis (MD). Some of these disorders are mainly caused by the imbalance of the neurotransmitter levels or the disturbance in its function. Neurotransmitters are basically messengers, molecules in the nervous system are used to transmit messages between neurons through synapses.

Alzheimer's disease is a cognitive disorder, where About 55 million people have dementia, and %60 of this population has Alzheimer's disease. The onset stage of this disease is memory loss, and in later stages, the patients could have problems with speaking, eating, and swallowing or the disability to walk.

Yet the neurological disorders in some cases of its distributions are in some point revolve around human actions and habits such as diet and how it could increase the chances of Alzheimer's disease development. This paper will focus on contributing relations and mechanisms in terms of represented information on the impact of diet on Alzheimer's disease and presenting relations between different variables that have an important role in the study, variables due to diet impact such as oxidative stress others belong to Alzheimer's disease causes such as

amyloid beta, and acetylcholine. The study contributes to the relationship between these variables and their significant role in the case of Alzheimer's disease and diet.

i. Inflammatory Diet

The body's natural, important defense against microbial infections, tissue damage, and trauma is called inflammation. It supports the body's ability to recover from injury and protect itself. Inflammation promotes the immune response by enlisting innate immune cells that are capable of producing inflammatory cytokines (i.e., signaling proteins). Particularly, the innate immune system of the body is under the control of the gene transcription factor kappaB (NF-κB). However, Inflammation can be harmful if it persists for a long time. When (NF-κB) is continuously activated as a result of consuming inflammatory food, inflammation becomes chronic. Chronic inflammation causes a dysregulated immune response, which disturbs physiological functions that are meant to be homeostatic.

Inflammation hugely contribute to causing diseases such as inflammatory bowel disease (IBD), diabetes mellitus, asthma, cardiovascular diseases, depression, Alzheimer's disease (AD), and different types of cancer[1]

Inflammatory and anti-inflammatory foods: Diet can influence different stages of inflammation. Inflammation can result from being exposed to environmental toxins, aging, or chronic stress.

On one hand, the over consuming of inflammatory foods can cause inflammation, including red meat, processed meat, snack cakes, pies, cookies and brownies, bread and pasta made with white flour, deep-fried items – French fries and fried chicken –, and high-sugar food – such as candy, jelly, syrup, soda, bottled or canned tea drinks, and sports drinks.

On the other hand, healthy eating patterns help put inflammation down and stay healthier. These patterns can be achieved through being committed to consuming particular types of supplements found in food, including Omega-3 – found in different types of fish, nuts, and seeds-, Vitamin C – found in fruits and vegetables –, and polyphenols – found in the wise consuming of tea, coffee, and dark chocolate.[2]

ii. Neurotransmitters

Mechanism: Neurotransmitters are the nervous system's way of delivering messages to the rest of body organs and parts through nerve cells. Each neurotransmitter is responsible for a function, which may be moving a certain muscle, activating memory or appetite, controlling blood pressure, …. etc. [3]

They are also involved in the processes of early human development, including neurotransmission, differentiation, the growth of neurons, and the development of neural circuitry [9]. Certain neurotransmitters may appear at different points of development. For example, monoamines, neurotransmitters responsible for controlling basic emotions and affecting major depressive disorders, are present before the neurons are differentiated [9].

At presynaptic nerve terminals, neurotransmitters are primarily released via vesicular action. Neurotransmitters are released into the synaptic cleft mainly via calcium-evoked exocytosis of presynaptic vesicles. The neurotransmitter-containing vesicles are attached to the plasma membrane by active zones, specialized regions on the presynaptic plasma membranes. Action potentials cause calcium to enter the presynaptic cleft, which causes the active zones to fuse with the vesicles and release neurotransmitters. The fusion of neurotransmitter-containing vesicles and the active zone is mediated by several proteins. The exocytosis of neurotransmitters from the presynapse may be inhibited and activated as well by these proteins; Synaptobrevin-2, SNAP-25, and syntaxin-1 collectively make up the soluble N-ethylmaleimide sensitive factor attachment protein receptors (SNAREs), which are essential for membrane fusion and ultimately exocytosis. [4]

Acetylcholine and Serotonin: The neurotransmitter acetylcholine (ACh) is primarily responsible for memory-related processes. Furthermore, it is crucial for cognitive, memory, and learning processes in brain nerve cells. It moves voluntary muscle, muscle movement you control, all over the human body by binding to muscarinic receptors. It also regulates heart contractions and blood pressure, lowers heart rate, moves food by contracting intestinal muscles, increases stomach and intestine secretions, causes glands to secrete substances like tears, saliva, milk, sweat, and digestive juices, regulates the flow of urine, and contracts muscles that control nephrons.

On the other hand, it causes skeletal muscle to contract by binding to nicotinic receptors, which releases adrenaline and norepinephrine from the adrenal glands, activating the sympathetic nervous system in humans. [5]

Serotonin, also referred to as 5-hydroxytryptamine (5-HT), is a monoamine neurotransmitter. In addition to its hormone-like properties, it plays a part in morphogenesis, the biological process by which both body structure and form emerge during embryonic development. It also has a significant impact on a number of other bodily processes, such as mood regulation (when serotonin levels are normal, you feel more alert, emotionally stable, happier, and calmer, and vice versa), regulating sleep (along with dopamine, serotonin helps the brain regulate how well and how long a person sleeps), wound healing (serotonin narrows blood vessels, which slows blood flow and causes clots to form), and bone density (high levels of serotonin lead to weak bones and vice versa). [6]

iii. Alzheimer's disease

Alzheimer's disease is a progressive brain disorder that deteriorates with time, characterized by significant changes in the brain due to the accumulation of certain protein deposits. This process ultimately leads to brain atrophy and, in some cases, brain cell death [13]. Gradual decline in memory, cognitive abilities, and social skills is a hallmark of Alzheimer's, making it the leading cause of dementia [13].

In the United States, approximately 6.5 million individuals aged 65 and older live with Alzheimer's disease, with more than 70% of them being 75 years or older [14]. Globally, of the roughly 55 million people living with dementia, an estimated 60% to 70% are believed to be affected by Alzheimer's disease [14].

On a global scale, the year 2020 witnessed over 55 million individuals grappling with dementia. According to data from Alzheimer's Disease International (ADI), the number of people afflicted with dementia has nearly doubled approximately every two decades [14].

The primary symptom associated with Alzheimer's is memory loss. In its early stages, individuals with the disease may recognize their struggles with memory recall and clear thinking. Alzheimer's-induced changes in the brain progressively lead to challenges in six key areas: memory, cognitive abilities, decision-making, planning and executing tasks, behavioral shifts, and the loss of fundamental skills [12].

However, according to (ADI) research, the majority of people who are now living with dementia have not received a formal diagnosis. Only 20-50% of dementia cases are recognized and documented in primary care in high-income nations [14]. This treatment gap is undoubtedly considerably wider in low and middle-income nations, with one research in India claiming that 90% of patients go misdiagnosed [14]. If these figures are extrapolated to other nations, it appears that almost three-quarters of people with dementia have not been diagnosed, and hence do not have access to the treatment, care, and organized support that a formal diagnosis may bring. Alzheimer's disease patients typically live between

three and eleven years after diagnosis [14]. However, some people survive for 20 years or more [13]. The degree of disability at the time of diagnosis can have an impact on life expectancy [13]. Untreated vascular risk factors, such as hypertension, are linked to a higher rate of Alzheimer's disease progression [12].

Alzheimer's disease is classified into five detailed stages:

The first stage: Preclinical Alzheimer's disease: During this time, neither the patient nor those around them will notice any symptoms [12]. This stage of Alzheimer's can last for years, possibly even decades. New technologies can identify the tangles development, which develop when tau proteins change shape and organize into structures. These are hallmarks of Alzheimer's disease [12].

Additional biomarkers for Alzheimer's disease have been discovered. These are present in blood tests and may suggest a higher risk of disease [12]. These biomarkers can be used to help confirm an Alzheimer's disease diagnosis, usually after symptoms develop [12]. Newer imaging techniques, biomarkers and genetic tests will become more important as new treatments for Alzheimer's disease are developed [13].

Second stage: Mild cognitive impairment due to Alzheimer's disease: Mild cognitive impairment causes minor deficits in memory and thinking skills [12]. These modifications aren't large enough to have an impact on job or relationships [12]. Memory lapses may occur in people with MCI when it comes to knowledge that is normally easily remembered [12]. This could include recent discussions, activities, or appointments.

Individuals with Mild Cognitive Impairment (MCI) may also encounter challenges in gauging the time needed for various activities. Estimating the number or sequence of steps required to complete a task can become problematic, and making well-informed decisions might grow more challenging [12].

It's important to note that not everyone with MCI progresses to Alzheimer's disease. Typically, MCI is diagnosed based on a thorough assessment of symptoms and the clinical judgment of healthcare professionals. However, if necessary, the same diagnostic tests employed to identify early-stage Alzheimer's disease can also be used to ascertain whether MCI is a result of Alzheimer's disease or another underlying cause.

Moving on to the third stage: Mild dementia attributed to Alzheimer's disease. Alzheimer's disease is often recognized during the initial phases of mild dementia. At this point, both family members and medical professionals observe significant difficulties in memory and cognitive reasoning [12]. These symptoms notably impede everyday functioning.

This stage of detecting memory loss of recent activities, trouble with problem solving and sound judgment, changing personality, and getting lost or misplacing belongings [12].

Fourth stage: Moderate dementia due to Alzheimer's disease: People get more confused and forgetful during the moderate dementia stage of Alzheimer's disease. They begin to require more assistance with daily activities and self-care [13].

Fifth stage: Severe dementia due to Alzheimer's disease: It is the late stage of Alzheimer's disease, where mental function continues to decline. The disease is also having an increasing impact on movement and physical capacities [12].

Patients in this stage lose the ability to communicate, and experience a decline in physical abilities, for instance, they cannot walk without assistance [12]. Moreover, they require daily assistance and personal care [13].

II. Methods

The study contributes the different relation between variables and how these variables impact each other to better understand the mechanism of Alzheimer disease, with a clear understanding of these relations, the study could demonstrate the significant impact of diet on Alzheimer's Disease. The aim connection is between diet and Alzheimer's Disease, the variable relation is the connection dots which start with Amyloid- β as the key role in Alzheimer's disease pathogenesis and considering the role of the neurotransmitters. On the other side of the study, the diet has various styles with each having its significance though this study contributes the diet styles that have a significant correlation with Alzheimer's disease, in terms of the diet styles such as vegetarian diet that cause oxidative stress which is responsible for the inflammation and neurodegenerative disorders in the neurons. The significant contribution is the experimental data of the vegetarian diet food and its impact on disturbing vitamins and mineral levels in the body, in that matter, vitamins deficiency such as vitamin B12 and vitamin D that vegetarian diet food lack, these vitamins absent or deficiency could increase the risk of Alzheimer's disease.

I. Role of Amyloid- β in Alzheimer's disease pathogenesis

Amyloid β (Aβ) is considered a critical reason for the development of Alzheimer's disease (AD) the senile plaques (SPs) and intracellular neurofibrillary tangles (NFTs), which results in the loss of neurons and synapses. The SPs are formed by aggregation of (Aβ) as some studies propose that it is a small protein composite of 39-43 amino acids [18].

At (B) phase in Figure 1: represents the two cleavage processes of Amyloid precursor protein (APP), it is a transmembrane glycoprotein with a large luminal domain and a short cytoplasmic domain. In processing of cleaving the (APP) and Aβ formation, APP could go through either an amyloidogenic or non-amyloidogenic pathway [18].

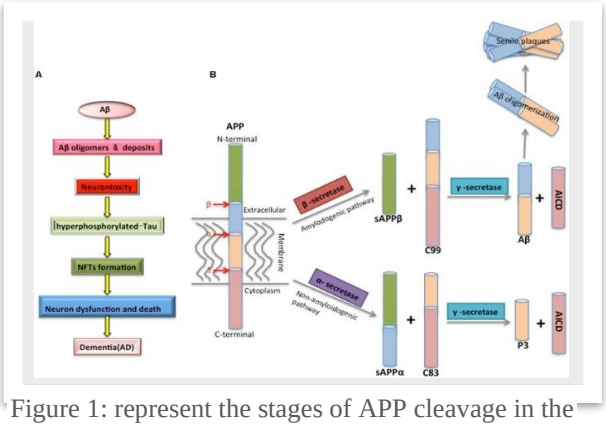

Figure 1: represent the stages of APP cleavage in the neuron membrane

The amyloidogenic pathway is the process of Aβ formation, in this pathway APP is firstly cut by β-secretase, producing soluble β-APP fragments (APPβ) and a C-terminal β fragment (C99), C99 is further cut by γ-secretase, generating APP intracellular domain (AICD) and Aβ as a non-soluble fragment [3].

The non-amyloidogenic pathway is another way to prevent the formation of Aβ, as APP is firstly cut by α-secretase within the Aβ domain, producing soluble α-APP fragments (APPα) and C-terminal fragment α (C83), C83 is then cleaved by γ-secretase [3].

i. Biochemistry of Amyloid β-Protein and Amyloid Deposits in Alzheimer's Disease

Figure 2: code sequence of amyloid plaques

Amyloid (A) is a 39-43 residue amyloidogenic peptide that is deposited in the extracellular amyloid plaques [6], whose 1-letter code sequence is shown in **Figure 2**. That defines the brain of people with Alzheimer's disease (AD). On chromosome 21, there is the gene for amyloid beta precursor protein. Moreover, it is formed by the

enzymatic cleavage of APP, the Amyloid Precursor Protein, a type-1 transmembrane protein produced in many organs, particularly the central nervous system (CNS) [6].

According to some studies on modern research on the fundamental mechanism of Alzheimer's disease (AD). The meningovascular amyloid subunit in Down's syndrome brains was the same "β-protein," as they had dubbed it. Glenner drew attention to this evidence of a crucial biochemical link between Down's syndrome and AD, a theory he had championed in a foresighted paper in Medical Hypotheses as early as 1979 (Glenner 1979) [15]. Glenner reasoned that since trisomy 21 caused an accumulation of Alzheimer-type A in arteries and plaques, familial AD may well be caused by a deficiency in the -protein precursor on this chromosome. Glenner omitted to mention the variability of familial types of AD and the possibility that many cases may not be genetically determined, at least at the time.

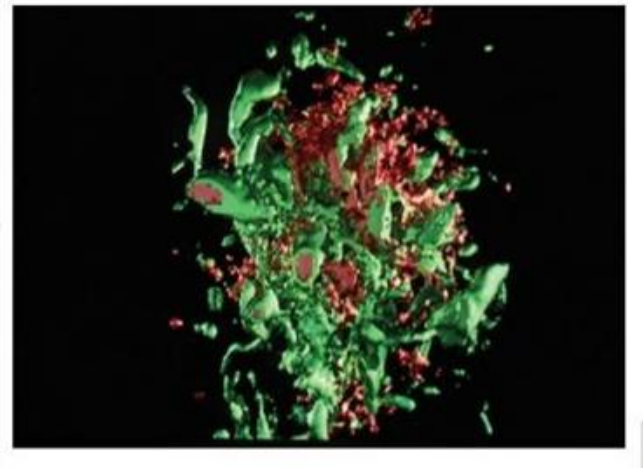

Figure 3: microscopy image of a neurotic (senile) plaque in the cortex of an Alzheimer's patient

Figure 3 represents a Confocal microscopy image of a neurotic (senile) plaque in the cortex of an Alzheimer's patient that has been three-dimensionally rebuilt. Amyloid -protein is colored red by an antibody to identify extracellular amyloid, and tau is colored green by an antibody to reveal closely related dystrophic neurites. The plaque core, it should be noted, is not a single, porous mass of amyloid, but rather is broken up and contains aberrant cell processes intercalated therein [8].

ii. Amyloid beta and acetylcholine

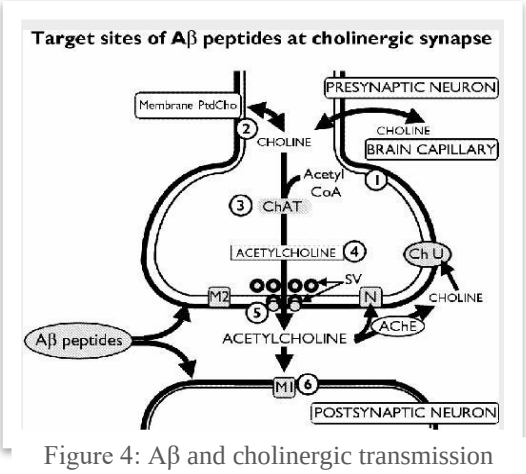

Figure 4: Aβ and cholinergic transmission

Figure 4 shows the Targets of Aβ that modulate cholinergic transmission:

(1) Aβ reduces the activity of pyruvate dehydrogenase, an enzyme that generates acetyl coenzyme A (CoA) from pyruvate, (2) Aβ reduces high-affinity uptake of choline; (3) long-term or high-dose exposure to Aβ reduces activity of the choline acetyltransferase (ChAT) enzyme; (4) Aβ reduces acetylcholine (ACh) content; (5) Aβ reduces ACh release from synaptic vesicles (SV); (6) Aβ impairs muscarinic M1-like signaling. AChE = acetylcholinesterase, Ch U = site of choline uptake, M2 = presynaptic muscarinic M2 receptor, N = presynaptic nicotinic receptor, PtdCho = phosphatidylcholine.[16]

The studies of APP and Aβ [17], suggest the notion that overexpression levels of Aβ peptide, and the aggregation of Aβ that cause subcellular alterations or neuronal loss in selected brain regions. The great levels of Aβ peptide may incentivize the formation of neurofibrillary tangles in tau in some experiments on mice[18]. Furthermore, these results suggest that Aβ peptides have a role in the neurodegenerative process in which the nerve cell loses its function and dies.

Degeneration of neurons and synapses in the brain along with AD, could be located within regions that contain high levels of plaques and tangles [17]. Regions include the hippocampus, entorhinal cortex, amygdala, neocortex, and basal forebrain cholinergic neurons, Biochemical investigations indicated that there are neurotransmitters including acetylcholine (ACh), serotonin, noradrenaline, and somatostatin, as they are differently related with AD [4].

The findings include a reduction in the activity of the ACh-synthesizing enzyme, and choline acetyltransferase (ChAT) [17], in the neocortex, which correlates with dementia. Reduced choline absorption, and ACh loss of cholinergic neurons from the basal forebrain region it was hypothesized that is due to the inactivity of acetylcholine could cause a cholinergic deficit in the hippocampus and neocortex of brains of those with AD and these cholinergic neurons is either spared or affected in the late stages of the AD[17].

Basal forebrain cholinergic neurons loss has led to the study of ACh receptors in the brains of AD patients. ACh affects the central nervous system by interacting with G-protein-coupled muscarinic and ligand-gated cation channel nicotinic receptors. Five distinct muscarinic receptor subtypes, m_1–m_5. Studies suggest that AD patients have a decrease in muscarinic receptors in their brains.

III. Results

i. Vegetarian diet lack of vitamins associated with AD.

The vegetarian diet is a diet style based on consuming plant-based food, however, this diet style may be beneficial in many aspects but it was noticed that this type of diet may increase the risk of some cognitive diseases such as Alzheimer's disease, due to the plant-based food lack of some essential vitamins such as vitamin D and vitamin B12.

Vitamin B12, are essential water-soluble micronutrients that have to be consumed in sufficient quantities in the diet. They are necessary for preserving hematopoiesis and the health of neurons [11]. In affluent nations, vitamin B12 insufficiency is uncommon, although it is widespread and affects 10 to 15% of people over the age of 60 and 25 to 35% of people over the age of 80 [11]. The antioxidative property of vitamin B12, with B12 deficiency, might lead to the oxidation of lipids, proteins, and nucleic acids and so it could contribute to the development of age-related diseases, in which oxidative stress is a major factor, including AD [10], and Parkinson's disease.

In which the different processes that were explored on how vitamin B12's antioxidant effects work, including direct scavenging of ROS, particularly superoxide in the cytosol and mitochondria, and indirectly increasing ROS scavenging via maintaining glutathione levels [10]. Additionally, vitamin B12 may offer defense against oxidative damage brought on by inflammation. Vitamin B12 reduction is associated with an increase in interleukin-6 production and TNF-α levels. Interleukin-6 has a role in inducing hyperphosphorylation of tau and TNF-α increases the Aβ burden by upregulating β-secretase production and increased γ-secretase activity [10].

A study was done on 15 different groups [11], with the objective of finding a positive result on vitamin B12 deficiency and the increase in oxidative stress. This study is a collection of different scientists' studies on this topic, the data were based on experiments from different countries in India, Egypt, Romania, Turkey, Italy, Oman, and Jordan.

These studies were based on some common terms of vitamin B12 markers and oxidative stress biomarkers such as MDA, GSH, TAC, TAS, and SOD that basically support increased oxidative stress or reduced antioxidant capacity in case of lower B12 status.

In these data there were different study cases of the 15 groups: there were two retrospective studies (RS),

two cross-sectional studies (CS), and seven case-control studies (CC).

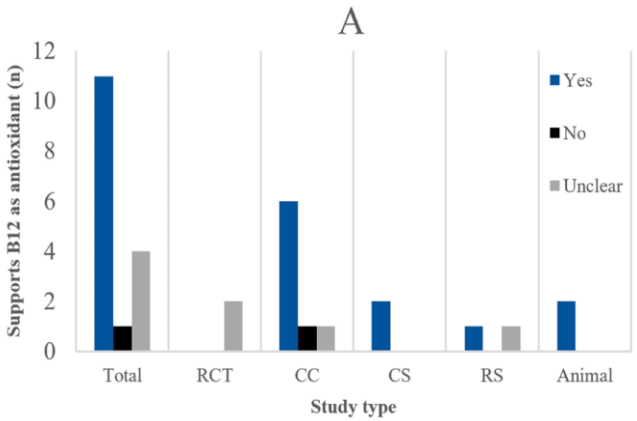

Figure5: the Number of studies that overall support, do not support, or show unclear results regarding the antioxidant properties of B12, in total and per study type.

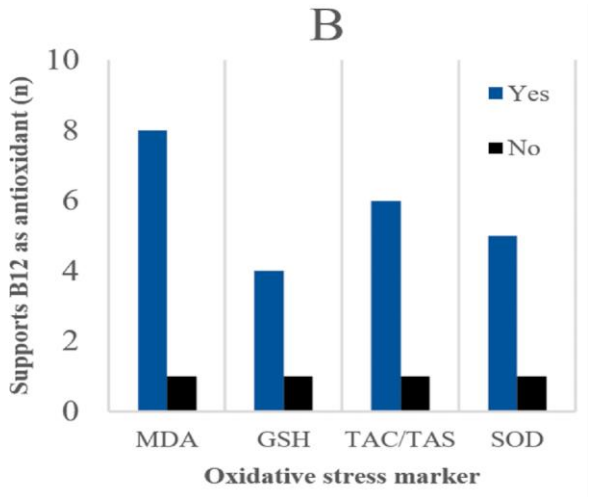

Figure 6: Number of statistical tests for all study types for common oxidative stress biomarkers that significantly ($p < 0.05$) support increased oxidative stress or reduced antioxidant capacity in case of lower B12 status.

The study results showed that the majority of the experiments contribute to the main objective.

Nine out of 15 studies supported the antioxidant properties of B12 (60%). One did not (6.7%). Five showed unclear results (33.3%). As shown in **Figure 5** [11].

Five CC studies, one CS, one RS, and two animal studies supported B12 as an antioxidant. Notably, the potential antioxidant effect of B12 was unclear for both RCTs due to their broad-spectrum micronutrient interventions. As shown in **Figure** 6 [11].

IV. Discussion

i. Oxidative stress

Oxidative stress is a condition caused by an imbalance between production and accumulation of oxygen reactive species (ROS), including superoxide radicals (O_2), hydrogen peroxide (H_2O_2), hydroxyl radicals (OH), and singlet oxygen ($^1O_2$), in cells and tissues and the ability of a biological system to detoxify these reactive products. The majority of ROS are produced by mitochondria. Cellular respiration, the lipoxygenases (LOX) and cyclooxygenases (COX) involved in the metabolism of arachidonic acid, as well as endothelial and inflammatory cells, can all produce O2 [5].

Environmental stressors, including UV, ionizing radiation, pollutants, heavy metals, and anti-stress medications also contribute to increasing ROS levels, which lead to the occurrence of oxidative stress. Numerous diseases, including Parkinson's disease, Alzheimer's disease (AD), amyotrophic lateral sclerosis (ALS), multiple sclerosis, depression, and memory loss, have been linked to oxidative stress; oxidative stress plays a role in the loss of neurons and development of dementia in Alzheimer's. The toxic peptide β-amyloid, which is produced by free radical action and frequently found in the brains of AD patients, is at least partially responsible for the neurodegeneration seen during the onset and progression of AD [11].

ii. Oxidative stress and the amyloid beta peptide in Alzheimer's disease

Oxidative stress is known to play an important role in the pathogenesis of a number of diseases [7]. It is specifically associated with the etiology of Alzheimer's disease (AD), an age-related neurodegenerative illness that is the leading cause of dementia in the elderly. Furthermore, AD is characterized by intracellular neurofibrillary tangles and extracellular production of senile plaques formed of aggregated amyloid-beta peptide (A) and metal ions such as copper, iron, or zinc [5][6].

Active metal ions, for example, copper, can speed up the production of Reactive Oxygen Species (ROS) when bound to the amyloid-β (Aβ). Thus, ROS can be produced in the hydroxyl radical, which is the most reactive one, which may lead to oxidative damage on both the Aβ peptide and surrounding molecules (proteins, lipids, etc....) [7].

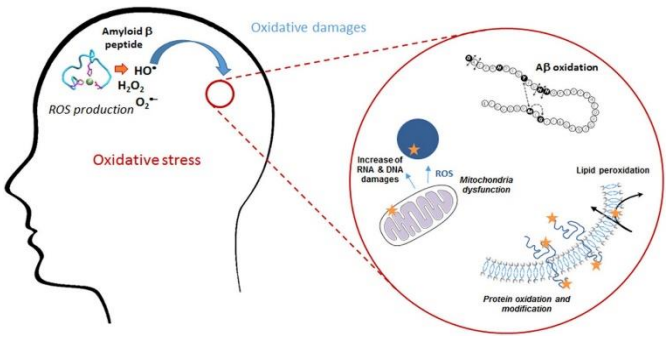

Figure 7: shows the detailed process of the oxidative damage.

Given the importance of oxygen, the many systems for producing and eliminating ROS, and their regulation, it is not surprising that oxidative stress has been linked to a wide range of disorders. Furthermore, oxidative stress can become a vicious cycle, as the created ROS can degrade biomolecules, leading to further ROS accumulation. For example, when ROS attack metalloproteins, they can cause the release of redox-competent metal ions, leading to an increase in ROS production. Additionally, the brains of people suffering from neurodegenerative disorders such as Alzheimer's and Parkinson's reveal oxidative damage, and oxidative stress appears to be a factor in many of them. Because the brain consumes so much dioxygen (20% of total body consumption), it may be especially vulnerable to oxidative damage under oxidative stress [6].

Apart from the global reduction in the brain volume, one of the hallmarks of Alzheimer's disease is the existence of amyloid plaques in the brain, which is caused by the "deposition of a special substance in the cortex," as first described by Alos Alzheimer. These plaques, also known as senile plaques, are seen in the extracellular space of the AD brain, notably in the hippocampus. They are predominantly made up of a peptide called Amyloid-(A), which aggregates and produces mostly -sheet rich fibrils. The existence of intracellular neurofibrillary tangles in the brain [3], which are also seen in Parkinson's disease (PD) and are made up of hyperphosphorylated Tau protein, is another feature of the disease. To stabilize microtubules, this microtubule-associated protein typically interacts with tubulin.

Metal ions such as zinc, iron, and copper are found in the brain, as previously stated. They are required to modulate neuronal activity in synapses and are engaged in metallo-protein biological processes. Metal ion homeostasis is impaired in various illnesses, including Alzheimer's, and concentrations and distribution are far from normal. Cu and Zn levels, in particular, can reach up to three times the typical levels found in healthy brains. Furthermore, amyloid plaques isolated from AD brains contain a significant concentration of these metal ions. Because they can bind to A at physiological concentrations, their coordination modalities are of interest in understanding their function in Alzheimer's disease [6].

ROS are radicals and molecules formed when molecular oxygen is incompletely reduced. They are created in modest amounts during the in vivo metabolism of oxygen, via four sequential 1-electron reductions of O2 that result in the creation of H2O. They are required for cell homeostasis and play a

crucial role in signaling, but they are also reactive oxidants that can damage biomolecules [6].

iii. Oxidative stress and diet

Reactive Oxygen Species (ROS) and Reactive Nitrogen Species (RNS), which are involved in metabolism, development, and stress response, are essentially what produce oxidative stress. This unbalanced state may cause oxidative damage by oxidative modification of cellular macromolecules, structural tissue damage from cell death via necrosis or apoptosis, and cell death via apoptosis. ROS are highly reactive molecules with unpaired electrons that can affect how biological processes work. Proteins, lipids, and nucleic acids may undergo structural and functional damage as a result of oxidative stress.

Oxidative stress is basically caused by mitochondria via oxidative phosphorylation that generates intracellular ROS. Meanwhile, ROS causes a mitochondrial malfunction. The NADPH oxidase family (NOX) and oxidative phosphorylation in mitochondria are the main sources of H2O2. For an organism to remain in a healthy state, the proper ROS are required. However, excessive ROS has been linked to a variety of health issues, such as obesity, cancer, cardiovascular disease, and neurological illnesses.

Cognitive diseases such as Parkinson's disease and Alzheimer's disease are examples of neurodegenerative diseases that affect the elderly. They are characterized by a progressive loss of neuron cells and diminished mobility or cognitive function. Mitochondrial dysfunction is one of these disorders' key traits. To supply the energy requirements for cellular functions, particularly the synthesis of neurotransmitters and synaptic plasticity, the mitochondria in neurons have a crucial role. Increased mitochondrial permeability, mitochondrial disorganization, oxidative damage to mtDNA, weakened antioxidant defenses, and shortening of telomeres are all associated with mitochondrial dysfunction. Due to their high energy needs, high fatty acid content, high mitochondrial density, and low bioavailability of antioxidant compounds and antioxidant therapy, neurons are particularly vulnerable to oxidative stress. In Alzheimer’s disease, Aβ aggregation causes Ca2+ release from the endoplasmic reticulum to the cytoplasm, which could lead to a decrease in the accumulation of ROS. Neuronal functions are impaired, which further leads to neuroinflammation and neuronal loss.

Diet can control mitochondrial disease. A study found that patients with Lennox-Gastaut syndrome (LGS), a common form of refractory epilepsy, with mitochondrial dysfunction, experienced a significant clinical improvement in both seizures and cognitive performance. Patients with heart failure benefit from taking more docosahexaenoic acid (DHA), an n-3 polyunsaturated fatty acid. By binding to membrane phospholipids, lowering the viscosity of mitochondrial membranes, and speeding up the uptake of Ca2+, DHA supplementation can enhance the DHA content in mitochondrial phospholipids, preventing the onset of left ventricular failure.

Unpaired electrons are produced by cells during regular cellular respiration as well as under stressful conditions, usually via oxygen- or nitrogen-based byproducts. These highly unstable pro-oxidant compounds have the potential to oxidize nearby biological macromolecules. Over time, the development and buildup of reactive pro-oxidant species can harm lipids, carbohydrates, proteins, and nucleic acids. This oxidative stress has the potential to exacerbate a number of age-related degenerative disorders, including Alzheimer's and Parkinson's.

There are various diet styles and one of the most common diet styles is the Western diet, which is considered by the high intake of saturated fats, highly refined carbohydrates, and animal-based protein and a deficiency in the consumption of plant-based fiber. It has been shown that people who eat a Western diet food are more likely to develop chronic disease and have higher levels of oxidative stress. In the Western diet style, consuming too much fat

causes oxidative stress, mitochondrial damage, and inflammation. High-calorie diets disrupt redox processes, accelerating aging signs and raising the risk of chronic diseases.

Antioxidants that include vitamins, and minerals can counteract this oxidative damage as they play a role in protecting the cell from free radicals such as ROS and RNS. Therefore, diet plays a crucial role in health, via specific food consumption that could disturb antioxidant levels in the body, therefore affecting cellular function and disease risk, emphasizing the importance of balanced nutrition and lifestyle interventions.

V. Conclusion

In conclusion, this research adds to our understanding of the complex interactions between nutrition, inflammation, neurotransmitters, and oxidative stress in Alzheimer's disease. It underlines the importance of dietary and lifestyle changes in lowering the risk of Alzheimer's disease and lays the groundwork for future research into targeted therapeutics. As we continue to learn more about the complexity of neurodegenerative disorders, a multifaceted strategy that includes nutrition, neurobiology, and oxidative stress management may hold the key to a better future for people at risk of Alzheimer's disease.

Our research has revealed numerous crucial findings, offering light on prospective routes for additional investigation and therapeutic approaches. Our findings highlight the significant role of nutrition in the development and progression of Alzheimer's disease. We've discovered that an inflammatory diet high in processed foods, red meats, sweet desserts, and high-sugar beverages promotes chronic inflammation, a known cause of AD. In contrast, we've highlighted the protective potential of anti-inflammatory foods like Omega-3 fatty acids, vitamins, and polyphenols, which may reduce the risk of AD.

Amyloid-β (Aβ), a key player in AD pathogenesis, has been explored in the context of its interactions with neurotransmitters and oxidative stress. Our findings suggest that Aβ accumulation can disrupt cholinergic and serotonergic neurotransmission, contributing to cognitive decline. Moreover, the interplay between Aβ, metal ions, and oxidative stress may accelerate neurodegeneration.

Oxidative stress emerges as a common denominator linking inflammatory diets, neurotransmitter dysregulation, and Aβ toxicity in Alzheimer's disease. The Overproduction of reactive oxygen and nitrogen species (ROS and RNS) causes cellular damage, notably in mitochondria, and contributes to neurodegenerative processes. Managing oxidative stress by food and antioxidants may provide therapeutic benefits.

Our findings highlight the possibility of dietary treatments in reducing the risk and course of Alzheimer's disease. Individuals who follow an anti-inflammatory diet may reduce chronic inflammation, support neurotransmitter balance, and combat oxidative stress, boosting brain health and memory preservation.

VI. References

[1] J. Alonso, M. Petukhova, G. Vilagut, S. Chatterji, S. Heeringa, T. Ustun, A. Alhamzaw, "Days out of role due to common physical and mental conditions: results from the WHO World Mental Health Surveys," Molecular Psychiatry, pp. 1-13, 2010.

[2] S. Kar, S. P. Slowikowski, D. Westaway, H. Mount, "Interactions between beta-amyloid and central cholinergic neurons: implications for Alzheimer's disease," Journal of Psychiatry Neuroscience, pp. 427-41, 2004.

[3] X. Sun, W. Chen, Y. Wang, “β-Amyloid: the key peptide in the pathogenesis of Alzheimer’s disease”, Frontiers in Pharmacology, vol. 6, 2015. https://doi.org/10.3389/fphar.2015.00221

[4] Q. Huang, C. Liao, F. Ge, J. Ao, T. Liu, "Acetylcholine bidirectionally regulates learning and memory," Journal of Neurorestoratology, vol. 10, no. 2, 2022. https://doi.org/10.1016/j.jnrt.2022.100002

[5] S. Jiang, H. Liu, and C. Li, "Dietary Regulation of Oxidative Stress in Chronic Metabolic Diseases," *Foods*, vol. 10, no. 8, p. 1854, Aug. 2021. https://doi.org/10.3390/foods10081854

[6] C. Cheignon, M. Tomas, D. Bonnefont-Rousselot, P. Faller, C. Hureau, F. Collin, "Oxidative stress and the amyloid beta peptide in Alzheimer's disease", Redox Biology, vol. 14, pp. 450-464, 2018. https://doi.org/10.1016/j.redox.2017.10.014

[7] Z. Cai, B. Zhao, and A. Ratka, "Oxidative stress and β-amyloid protein in Alzheimer's disease", Neuromolecular medicine, vol. 13, pp. 223-250, 2011. https://doi.org/10.1007/s12017-011-8155-9

[8] C. L. Masters, D. J. Selkoe, "Biochemistry of amyloid β-protein and amyloid deposits in Alzheimer disease," Cold Spring Harbor perspectives in medicine, 2012. https://doi.org/10.1101/cshperspect.a006262

[9] P. T. Francis, "The Interplay of Neurotransmitters in Alzheimer's Disease," CNS Spectrums, vol. 10, no. S18, pp. 6–9, 2005. https://doi.org/10.1017/s1092852900014164

[10] E. van de Lagemaat, L. de Groot, and E. van den Heuvel, "Vitamin B12 in Relation to Oxidative Stress: A Systematic Review," *Nutrients*, vol. 11, no. 2, p. 482, Feb. 2019, https://doi.org/10.3390/nu11020482

[11] A. A. Lauer *et al.*, "Mechanistic Link between Vitamin B12 and Alzheimer's Disease," *Biomolecules*, vol. 12, no. 1, p. 129, Jan. 2022, https://doi.org/10.3390/biom12010129

[12] T. Karlsson, L. Bäckman, A. Herlitz, L.-G. Nilsson, B. Winblad, and P.-O. Österlind, "Memory improvement at different stages of Alzheimer's disease," *Neuropsychologia*, vol. 27, no. 5, pp. 737–742, Jan. 1989, doi: https://doi.org/10.1016/0028-3932(89)90119-x.

[13] P. Scheltens *et al.*, "Alzheimer's disease," *The Lancet*, vol. 388, no. 10043, pp. 505–517, Jul. 2016, doi: https://doi.org/10.1016/s0140-6736(15)01124-1.

[14] *Adi - dementia statistics Alzheimer's Disease International (ADI)*. https://www.alzint.org/about/dementia-facts-figures/dementia-statistics/ (Accessed: 10 May 2024).

[15] G. G. Glenner, "Congophilic microangiopathy in the pathogenesis of Alzheimer's syndrome (presenile dementia)," *Medical Hypotheses*, vol. 5, no. 11, pp. 1231–1236, Nov. 1979, doi: 10.1016/0306-9877(79)90005-7.

[16] A. Bordon, "Molecular mechanisms of Alzheimer's disease," 2017 https://api.semanticscholar.org/CorpusID:43715570

[17] S. Kar, S. P. M. Slowikowski, D. Westaway, and H. T. J. Mount, "Interactions between β-amyloid and central cholinergic neurons: implications for Alzheimer's disease," PubMed Central (PMC), Nov. 01, 2004. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC524960/

[18] J. Götz, F. Chen, J. Van Dorpe, and R. M. Nitsch, "Formation of neurofibrillary tangles in P301L TAU transgenic mice induced by AB42 fibrils," Science, vol. 293, no. 5534, pp. 1491–1495, Aug. 2001,

doi: 10.1126/science.1062097.