Smoking and Oxidative Stress: A New Lens to Consider Alzheimer's Disease

Karen Gipson[1] and Kendra E. Liu[2]
[1]American High School, California
[2]Neuroscience Graduate Program, University of Virginia, Virginia

Abstract

Smoking is a prevalent habit across the world, with about 2 billion individuals using tobacco products, typically in the form of smoking cigarettes. In the United States alone, there are an estimated 44 million active smokers. Smoking is recognized as a tremendous risk factor for various health conditions, such as CVD, COPD, stroke, and cancer, and emerging evidence demonstrates that it can also have detrimental effects on neurobiological aspects of the brain and cause neurocognitive abnormalities. Recent studies have shown that these smoking-related neural abnormalities can potentially serve as risk factors for Alzheimer's disease. Smoking itself can lead to an increased risk of Alzheimer's Disease and the progression of Alzheimer's pathology, and the extent of its effect can vary due to age and individual characteristics. This review explores the different neurobiological abnormalities that are caused by smoking, and its contribution to the pathogenesis of Alzheimer's Disease.

I. Introduction

Alzheimer's disease (AD) has captivated the scientific community for over a century, yet effective therapeutic interventions remain elusive (Lane et al., 2018). In 2021, the United States witnessed 6.2 million individuals aged 65 and older grappling with AD, a number anticipated to burgeon to a staggering 13.8 million by 2060, exerting tremendous strain on healthcare systems and families alike (Alzheimer's Association, n.d., 2021).

Clinically, AD manifests as cognitive dysfunction and memory deterioration, while its pathological underpinnings feature the emergence of senile plaques and neurofibrillary tangles (NFTs). The quest for understanding AD's etiological underpinnings has given rise to a myriad of hypotheses, encompassing the amyloid cascade, tau protein, inflammation, metal ions, and especially oxidative stress.

A common and prevalent source of oxidative stress is smoking tobacco. In the United States alone there are an estimated 46 million adults that smoke regularly (Cornelius et al., 2021). Smoking, notorious for its adverse health effects, introduces individuals to a host of noxious chemicals, many of which are potent instigators of oxidative stress. Inhalation of cigarette smoke unleashes a deluge of free radicals and reactive oxygen species (ROS) into the body (Pryor and Stone, 1993). Importantly, the influence of smoking-induced oxidative stress extends its malevolent reach to encompass the intricate terrain of the brain.

Frequent smoking causes an abundance of oxidative stress, contributing to the effect of AD (Ozguner et al., 2005). This review focuses on the intersection of AD, smoking, and oxidative stress. Smoking, a widely recognized agent of harm to health, extends its reach to encompass a potential link with AD susceptibility, a relationship that warrants careful scrutiny (Durazzo et al., 2014). The crux of this exploration rests upon the complex interplay between smoking-induced oxidative stress and its ramifications within the context of AD development.

II. Alzheimer's Disease (AD) defined and its significance

A. Prevalence of AD in the US and worldwide

AD is a prevalent and devastating neurodegenerative disease that has become a major global public health challenge. As the most common cause of dementia, AD affects millions of individuals worldwide, resulting in profound impacts on patients, their families, and society at large. AD has a slow progression, with an average lifespan of around 7 years after diagnosis for patients with AD. (Crimmins, 2015) The World Health Organization (WHO) estimates that approximately 50 million people are living with dementia in 2020, and it is projected that this number will continue to rise as the global population ages (Shin, 2022). According to the WHO's Global Dementia Observatory, the prevalence of dementia increases from approximately 5% in people aged 60-64 years to over 40% in those aged 90 or older. Additionally, an estimated 6.7 million Americans over the age of 65 have AD, and this number is projected to grow to about 13.8 million by the mid-century. While the number of deaths caused by stroke, heart disease, and HIV have all decreased, the number of deaths related to AD have increased more than 145%. (2023 Alzheimer's Disease Facts and Figures)

AD Risk Factors

Age is the single most significant risk factor for developing AD and the prevalence of AD rises exponentially with increasing age (Armstrong, 2019). While AD can affect individuals in their 40s or 50s, it primarily affects adults after the age of 65. Further, the risk of developing the disease doubles approximately every five years thereafter (Alzheimer's Association).

The link between aging and AD is multifaceted. As people age, there are various biological changes that occur in the brain, making it more vulnerable to neurodegeneration (Armstrong, 2019). One major change is the thinning of the cortical cortex across the brain, which is correlated with cognitive decline, as well as memory impairment. Additionally, the structural integrity of white matter volume begins to decrease quickly as people grow older, playing a pivotal role in cognitive decline. Aging also leads to ventricular enlargement, which can compress various blood vessels and destroy periventricular axons causing neuropsychological abnormalities. (Blinkouskaya et al., 2021) These changes that occur in the aging brain all lead to a decline in cognitive abilities. Ultimately, these biological changes may compound to increase an individual's susceptibility to the disease.

Sex differences in AD prevalence have been a subject of considerable research interest. It is widely recognized that females have a higher risk of developing AD compared to males (Pike, 2016). This disparity has led researchers to investigate potential biological and hormonal factors that might play a role in the onset and progression of AD. The association between estrogen, the primary female sex hormone, and AD risk has been an area of ongoing investigation. Estrogen has been shown to have neuroprotective properties and to play various roles in brain function, including memory and cognition. Some studies suggest that estrogen may protect against cognitive decline in females or even delay the onset of AD. In males, on the other hand, estrogen is not a significant factor in susceptibility of AD. Therefore, the relationship between estrogen and AD risk is complex and not fully understood. However, lower testosterone levels as a result of aging is a typical risk factor of AD. (Pike, 2016)

Genetic risk factors for AD also differentially affect females versus males. One example is the *APOE* ε4 allele that poses a greater risk for AD in females than for males (Pike, 2016). Studies with mice have demonstrated that the *APOE* ε4 allele has a stronger effect on cognitive decline in female mice than in male mice (Raber et al., 1998). Other factors, including differences in genetic susceptibility, lifestyle choices, and social and environmental influences, may also contribute to the gender disparity in AD prevalence. It is essential to conduct further research to gain a comprehensive understanding of the underlying mechanisms that contribute to the gender differences in AD.

AD represents a significant global health challenge, affecting millions of individuals worldwide. Its prevalence is expected to increase dramatically as the global population ages. While age remains the most significant risk factor for AD, sex plays crucial roles in AD's prevalence and manifestations. Addressing the impact of AD requires a comprehensive approach involving research, public health initiatives, and policies aimed at prevention, early detection, and support for affected individuals and caregivers.

B. Symptoms

Even during the subclinical stages of Alzheimer's, individuals may experience changes in mood, heightened anxiety levels, and increased sleep disturbances (Sprecher et al., 2017). These sleep disturbances can contribute to cognitive decline and worsen other symptoms. Sleep disturbances in Alzheimer's are linked to alterations in the brain's sleep-wake regulatory centers (Musiek et al., 2015). Depressive symptoms, apathy, and social withdrawal are particularly common during this phase. These symptoms can significantly impact the overall well-being and quality of life for individuals in the early stages of the disease. (Sprecher et al., 2017)

The presentation of AD symptoms can vary significantly from patient to patient. Many later-stage Alzheimer's patients undergo significant behavioral changes, arising from neurodegeneration in many different brain areas. Symptoms including mood swings, agitation, aggression, and irritability, which causes patients to withdraw from social activities and lose interest in previously enjoyed hobbies. These often result from alterations in the brain's limbic system, which governs emotions and behaviors. (De-Paula et al., 2019) Another symptom of Alzheimer's is a decrease in the initiative and motivation to engage in activities. Patients may become passive and require prompting to initiate tasks or conversations. (Klionsky et al., 2019)

As the disease progresses, individuals may struggle with finding the right words, following conversations, or understanding complex language. Speech may become hesitant and repetitive. Language difficulties are attributed to the degeneration of language centers in the left hemisphere of the brain, such as in Broca's area and Wernicke's area. (Wilkins et al., 2017) Additionally, there is neurodegeneration in the parietal and occipital lobes, causing AD patients to have limited visuospatial abilities. This leads to difficulties in judging distances, recognizing familiar objects, or navigating familiar environments. (Boxer et al., 2015) Damage to the prefrontal cortex leads to impaired executive functions, which involve planning, organizing, and problem-solving. This can lead to difficulties in managing daily activities and maintaining routines. (Alves et al., 2015) In some cases, individuals with Alzheimer's disease may develop neuropsychiatric symptoms, such as delusions and hallucinations. Neuropathological changes

in regions like the amygdala and medial temporal lobe contribute to the development of these symptoms (Hort et al., 2019).

Early detection and timely intervention are crucial for managing Alzheimer's disease effectively. Identifying these symptoms and seeking medical evaluation at the earliest signs can improve the quality of life for patients and their caregivers. Additionally, understanding the different presentations of Alzheimer's disease can aid in accurate diagnosis and the development of targeted therapeutic approaches.

C. Pathophysiology of AD: Understanding why it occurs

The etiology and pathophysiology of AD have been explored extensively, and likely involve multiple mechanisms (Imbimbo et al., 2005). AD was first described by Alois Alzheimer in 1901, based on a patient named Auguste D., who exhibited symptoms of paranoia, aggression, confusion, and memory loss. Alois Alzheimer's observations at autopsy, including brain shrinkage, plaques, and neurofibrillary tangles, laid the foundation for the understanding of AD. (Eratne et al., 2018)

For example, a prevalent hypothesis in AD research is the "β-amyloid cascade" hypothesis, which centers on the accumulation of amyloid-beta (Aβ) plaques in the brain. These plaques, composed of Aβ peptides, result from the processing of the amyloid precursor protein (APP). Aβ peptides play a central role in AD pathology by disrupting synaptic function, triggering inflammatory responses, and affecting neuronal health. APP can be metabolized through two pathways: the non-amyloidogenic and amyloidogenic pathways. The amyloidogenic pathway involves β-secretase and γ-secretase, generates Aβ, and leads to the formation of plaques. (Imbimbo et al., 2005)

Additionally, mitochondrial dysfunction and oxidative stress have emerged as critical components in the pathogenesis of AD (Tobore, 2019). Aβ has been observed to accumulate within mitochondria in living AD patients and in postmortem tissue samples. This suggests that mitochondrial dysfunction contributes to tau pathology and plays a crucial role in the etiopathogenesis of AD (Tobore, 2019). Mitochondria are major sources of reactive oxygen species and nitrogen reactive species. Mitochondrial dysfunction often results in overproduction of these species and/or failure of the antioxidant defense mechanisms, leading to oxidative and nitrative stress, which is closely associated with AD. Moreover, oxidative stress has been linked to the promotion of Aβ deposition, tau hyperphosphorylation, loss of synapses and neurons, and cognitive decline in AD (Tobore, 2019).

In summary, the mechanism of AD is characterized by the accumulation of Aβ plaques and neurofibrillary tangles. The role of mitochondrial dysfunction and oxidative stress in Aβ deposition, tau pathology, cognitive decline, and other aspects of AD underscores the complexity of this neurodegenerative disorder (Tobore, 2019). Understanding these mechanisms is crucial in the search for effective therapies for AD.

D. Oxidative stress and its role in AD

Defining Oxidative Stress

Oxidative stress is a multifaceted phenomenon that arises from the intricate interplay between fundamental chemical principles of oxidation-reduction and the complex biological concept of stress. Oxidation-reduction reactions play a fundamental role in signaling, energy production, and maintaining cellular homeostasis (Chen & Zhong, 2014).

At its core, oxidative stress involves the disruption of the delicate balance between the generation of reactive oxygen species (ROS) and the ability of cells and organisms to effectively counteract their potential harm (Chen & Zhong, 2014). ROS can break cell membranes and cause damage to the building blocks of cells, specifically the mitochondria (Shields et al., 2021). ROS encompass various chemical entities, including free radicals, oxygen metabolites like superoxide anion radical, hydrogen peroxide, hydroxyl radical, nitric oxide radical, and peroxynitrite, along with electronically excited states like singlet molecular oxygen (Chen & Zhong, 2014).

Contribution of Oxidative Stress to AD

Oxidative stress assumes a pivotal role in the intricate landscape of AD pathogenesis. The brain is a particularly susceptible organ to oxidative stress, primarily due to its elevated oxygen consumption and relatively diminished levels of antioxidant defenses (Sies, 2015). Within neurons, crucial components such as lipids, proteins, and nucleic acids become vulnerable to oxidative damage, thereby initiating a cascade of events that contribute to AD progression (Sies, 2015). Excess oxidative stress can lead to breakages in DNA and RNA (Salmon et al., 2005). Damaged DNA results in various mutations and can alter gene expression. Notably, DNA damage is elevated in the brains of AD patients (Ionescu-Tucker & Cotman, 2021).

The brain's vulnerability to oxidative stress is also due to its high oxygen consumption and the abundance of polyunsaturated fatty acids (PUFAs) in neuronal membranes (Chen & Zhong, 2014). PUFAs are particularly susceptible to oxidative damage, resulting in lipid peroxidation and the generation of harmful byproducts, including certain aldehydes (Chen & Zhong, 2014). These aldehydes have the potential to create bonds with vital proteins found in circulation or within cells. These oxidative events can disrupt neuronal membrane integrity and signaling, contributing to cognitive dysfunction observed in AD patients. (Barrera et al., 2018)

Furthermore, ROS-induced damage extends to proteins and nucleic acids. Protein carbonylation, a marker of oxidative damage to proteins, has been observed in the brain of patients with AD (Chen & Zhong, 2014). This oxidative modification can lead to functional impairment of crucial neuronal proteins. Additionally, oxidative stress leads to DNA and RNA oxidation, as evidenced by increased levels of oxidized nucleotides in AD patients (Chen & Zhong, 2014). These modifications sometimes disrupt genomic stability and gene expression, further exacerbating the neurodegenerative process in AD.

The emergence of oxidative stress in AD stems from a combination of factors, including mitochondrial dysfunction, augmented metal levels, inflammation, and the presence of Aβ peptides (Sies, 2015). These factors collectively contribute to ROS generation, which, in turn, contribute to the many features of AD pathology, such as DNA damage (Ionescu-Tucker & Cotman, 2021). The process involves the accumulation of Aβ plaques, the hyperphosphorylation of tau proteins, and the subsequent loss of synapses and neurons (Sies, 2015). Oxidative stress intersects with these pathological mechanisms of AD (Chen & Zhong, 2014). ROS promotes the aggregation of Aβ peptides and contributes to the formation of senile plaques (SPs), a hallmark of AD (Bai et al., 2022). Moreover, oxidative stress induces tau hyperphosphorylation, leading to the formation of neurofibrillary tangles (NFTs) (Bai et al., 2022). These pathological events collectively may contribute to synaptic dysfunction and neuronal loss in AD. The bidirectional relationship between oxidative stress and AD suggests that oxidative stress may act as both a contributor and a consequence of AD pathogenesis.

This intricate connection between oxidative stress and AD extends beyond correlation. Oxidative stress serves as a vital bridge that connects various hypotheses associated with AD etiology (Bai et al., 2022). This imbalance between pro-oxidants and antioxidants can perturb cellular function and contribute to the chronic neurodegeneration observed in AD (Sies, 2015). Enzymatic antioxidants like superoxide dismutase and catalase, along with non-enzymatic antioxidants, play a crucial role in maintaining redox balance (Bai et al., 2022). However, when the equilibrium is disrupted, the resulting oxidative stress can have cascading effects on cell signaling, gene expression, and overall neuronal health (Bai et al., 2022).

In conclusion, oxidative stress represents a crucial intersection between fundamental chemical processes and complex biological systems. It has emerged as a significant contributor to the pathogenesis of Alzheimer's disease, underscoring its intricate role in the progression of this devastating neurodegenerative disorder. The relationship between oxidative stress and AD is multidimensional, with oxidative stress both contributing to and being exacerbated by the underlying disease processes. As the understanding of oxidative stress continues to evolve, it holds the potential to serve as a target for therapeutic interventions aimed at mitigating the impact of AD on individuals and society at large.

III. Smoking and Its Effects

Delving deeper into the effects of smoking on the brain, it has become evident that this habit extends its influence beyond addiction and neurological alterations. Smoking has a profound impact on cognitive function and, intriguingly, an association with the development and progression of AD (Durazzo et al, 2014). This section explores the intricate relationship between smoking, cognitive decline, and the risk of AD, shedding light on the multifaceted consequences of this addictive behavior.

A. Prevalence of smoking and mortality rates

Prevalence in the United States

Despite considerable efforts to combat tobacco use, smoking has continued to be a significant public health issue in the United States (CDC, 2021a). According to the Centers for Disease Control and Prevention (CDC), approximately 14% of adults aged 18 years or older were current cigarette smokers in 2020 (CDC, 2021b). Though this represents a decline from

previous years, 19.1% in 2000, the absolute number of smokers remains high at 28.3 million Americans (CDC, 2023).

Among various demographics, certain age groups have been found to have a higher prevalence of smoking. For instance, a study conducted by Jamal et al. (2018) reported that adults aged 25-44 had the highest prevalence of current cigarette smoking at 16.8%. Additionally, individuals with lower socioeconomic status were more likely to smoke, as evidenced by findings from the National Health Interview Survey conducted by Schoenborn and Gindi (2019).

Mortality Rate in the United States:

Smoking has been consistently linked to an increased risk of mortality in the United States. A study published in the New England Journal of Medicine by Thun et al. (2013) estimated that smoking was responsible for approximately 480,000 deaths annually in the United States, making it the leading preventable cause of death.

Smoking also increases risk for various diseases such as heart disease, stroke, COPD, and other respiratory illnesses (Patra et al., 2018). Moreover, smoking also adversely affects the immune system, leading to increased susceptibility to infections and complications (Arcavi & Benowitz, 2004). Furthermore, exposure to secondhand smoke contributes to mortality rates as well as AD progression. According to a report by the Surgeon General of the United States (2014), more than 41,000 deaths per year are attributed to secondhand smoke exposure among nonsmokers. A study conducted by Jha et al. (2014) estimated that smoking reduces life expectancy by about 10 years, with significant variations depending on factors like smoking intensity, duration, and age of initiation.

B. Effects of Smoking on the Brain

Nicotine, the primary addictive component in tobacco, has a profound effect on brain function. After inhalation, nicotine rapidly crosses the blood-brain barrier and binds to nicotinic acetylcholine receptors in the brain (Benowitz, 2009). These receptors are widely distributed throughout the central nervous system, causing widespread effects when nicotine binds them that impact various biological and cognitive processes. In the brain, nicotine stimulates the release of several neurotransmitters, including dopamine, norepinephrine, and serotonin, leading to feelings of pleasure, increased attention, and enhanced mood (Picciotto & Kenny, 2013). This activation of the brain’s reward centers reinforces smoking behavior and contributes to the development of nicotine addiction.

Dopamine is a crucial neurotransmitter involved in the brain's reward system, and its regulation plays a vital role in addiction. Smoking significantly increases dopamine release in the brain's mesolimbic pathway, commonly known as the reward pathway (Volkow et al., 2010). Long-term smoking is associated with alterations in dopamine receptor availability and function (Kuhn et al., 2010). Chronic exposure to nicotine upregulates dopamine receptors, leading to neuroadaptive changes that reinforce the desire to smoke and make it difficult to quit. These

changes may contribute to the development of tolerance and dependence, making smokers require higher nicotine doses over time to achieve the same pleasurable effects.

Interestingly, research has revealed an intriguing similarity between brain regions targeted by smoking and Alzheimer's disease (AD). Both conditions involve brain regions critical for cognitive function and memory. Studies using positron emission tomography imaging have shown that smoking affects the hippocampus and the prefrontal cortex, regions also vulnerable to AD (Durazzo et al., 2014). The hippocampus is vital for learning and memory, while the prefrontal cortex plays a crucial role in decision-making and impulse control.

Moreover, smoking has been linked to increased oxidative stress and inflammation, which are implicated in the pathogenesis of AD (Mishra & Chaudhry, 2020). These findings suggest that smoking may contribute to cognitive decline and increase the risk of developing AD.

C. Age-related considerations:

Smoking has widespread health implications, and its relationship with age plays a significant role in determining its impact on health. In the United States, smoking remains prevalent, contributing to a substantial proportion of deaths due to smoking-related diseases. Understanding the age-related dynamics of smoking and its consequences is essential for comprehending its overall influence on public health. (Durazzo et al., 2014)

Smoking's prevalence is influenced by age, with notable variations across different age groups. The prevalence of adult smokers in the United States has remained relatively stable over the past five years. This consistency in prevalence suggests that smoking habits persist into adulthood for a significant portion of the population.

The health burden of smoking is substantial, leading to a range of smoking-related diseases that contribute to a considerable proportion of deaths. Cardiovascular disease, COPD, and cancer are some of the primary causes of mortality associated with smoking. Smoking's significant impact on productivity and overall health underscores the urgency to address its consequences. (Durazzo et al., 2014)

Numerous factors contribute to the risk of developing various health conditions, including smoking-related diseases. Several modifiable risk factors, such as smoking, are associated with adverse health outcomes. The interplay between age and smoking further complicates the risk profile for individuals, highlighting the importance of addressing smoking behaviors across the lifespan. (Durazzo et al., 2014)

Age is a critical factor in understanding smoking's impact on health. The relationship between smoking and health outcomes evolves as individuals age. The cumulative effects of smoking over time can increase health risks, making length of time smoking an essential consideration when assessing the consequences of smoking. (Durazzo et al., 2014)

Smoking's effects on health interact with other risk factors, potentially compounding the overall health risk. For example, the relationship between smoking and cardiovascular health is influenced by age, genetics, and other health behaviors. The impact of smoking-related oxidative stress on cellular function can be amplified by age-related physiological changes. (Durazzo et al., 2014)

While the negative health effects of smoking are well-established, quitting smoking at any age can lead to significant health improvements. Age, in this context, becomes a pivotal factor in determining the potential benefits of smoking cessation. Individuals who quit smoking can experience health benefits regardless of their age, underscoring the importance of encouraging smoking cessation efforts across all age groups. (Durazzo et al., 2014)

Age is a crucial determinant in understanding the intricate relationship between smoking and health consequences. The prevalence of smoking among different age groups, the age-related progression of smoking-related diseases, and the potential benefits of smoking cessation all emphasize the role of age in shaping the impact of smoking on public health. Addressing smoking behaviors at all stages of life is essential for reducing the overall health burden associated with smoking-related diseases. (Durazzo et al., 2014)

IV. Conjunction of AD & Smoking

Cigarette smoking is a well-established risk factor for numerous health conditions, including AD. Smoking introduces a multitude of toxic compounds into the body, many of which induce oxidative stress. Additionally, ROS generated by smoking may activate kinases responsible for tau hyperphosphorylation (Chen & Zhong, 2014), leading to the formation of neurofibrillary tangles (Bai et al., 2022). These processes collectively accelerate neurodegeneration in AD. Interestingly, there are notable similarities between the oxidative stress triggered by smoking and that observed in AD (Sies, 2015).

Firstly, smoking leads to increased levels of ROS and oxidative damage in various tissues and organs (Sies, 2015). The combustion of tobacco releases free radicals such as superoxide and other ROS, which can directly damage cellular components. Similarly, in AD, mitochondrial dysfunction, metal accumulation, inflammation, and Aβ peptides contribute to increased ROS levels, causing oxidative stress in the brain (Chen & Zhong, 2014). Smoking-induced oxidative stress contributes to the accumulation of Aβ plaques and the hyperphosphorylation of tau protein in the brain, both hallmark pathological features of AD (Chen & Zhong, 2014). The oxidative damage caused by smoking may facilitate the aggregation of Aβ peptides, promoting their deposition into senile plaques (SPs) (Bai et al., 2022).

Both smoking and AD are associated with alterations in antioxidant defense mechanisms. In smokers, there is a disruption in the balance between ROS production and the body's ability to neutralize these harmful molecules with antioxidants like superoxide dismutase (SOD) and catalase (Sies, 2015). Similarly, AD patients exhibit changes in the activities or expressions of antioxidant enzymes, including SOD, which may reduce the clearance of free radicals (Chen & Zhong, 2014). Moreover, smoking-related oxidative stress may interfere with synaptic plasticity

and neurotransmitter signaling, further impairing cognitive function in AD patients (Sies, 2015). The negative impact of smoking on vascular health and blood flow may exacerbate cerebral hypoperfusion, a common feature in AD (Sies, 2015).

In summary, smoking exacerbates oxidative stress in the brain by increasing ROS and decreasing antioxidants. This contributes to AD pathogenesis by promoting Aβ deposition, tau hyperphosphorylation, and synaptic dysfunction (Sies, 2015).

V. Conclusion

In this comprehensive review, we explored the intricate connections between smoking, oxidative stress, and Alzheimer's disease (AD). Smoking's prevalence in the United States has persisted as a significant public health challenge, with approximately 14% of adults being current cigarette smokers (CDC, 2021a, 2021b). Smoking has been consistently linked to increased mortality, with Thun et al. (2013) estimating it to be the leading preventable cause of death, responsible for approximately 480,000 deaths annually in the United States. Notably, smoking has also been associated with increased oxidative stress and inflammation, which are implicated in the pathogenesis of AD by contributing to Aβ accumulation, tau pathology, and synaptic dysfunction (Mishra & Chaudhry, 2020; Sies, 2015; Chen & Zhong, 2014).

Current investigations into the etiology of AD involves exploring the 'β-amyloid cascade' hypothesis and the role of mitochondrial dysfunction and oxidative stress (Imbimbo et al., 2005; Tobore, 2019). This complex web of relationships underscores the potential significance of smoking as a risk factor for AD, with oxidative stress acting as a central player connecting these intricate elements. In summation, the enigma of Alzheimer's disease continues to challenge our understanding of neurodegenerative disorders. As the prevalence of AD-related deaths escalates, the lack of treatment for AD is glaring (Srivastava et al., 2021).

The current FDA-approved therapies for AD, such as acetylcholinesterase inhibitors and N-methyl-D-aspartate receptor antagonists, while offering palliative relief, do not address the core pathogenesis of the disease (Srivastava et al., 2021). BACE1, as a primary therapeutic target for Aβ accumulation, has faced hurdles due to low bioavailability, serum half-life, and blood-brain barrier challenges (Srivastava et al., 2021). Failed clinical trials demonstrate the limitations of targeting single pathways, particularly the β-amyloid cascade, as AD pathogenesis is multifactorial and complex (Srivastava et al., 2021). The culmination of these clinical failures emphasizes the pressing need for innovative therapeutic approaches. Combining strategies, multi-targeted drugs that tackle the myriad symptoms and causes of AD, offer promise. The intricate web of connections between smoking, oxidative stress, and Alzheimer's disease underscores the potential significance of smoking as a risk factor for AD, with oxidative stress acting as a central player connecting these intricate elements.

Works Cited

A. Armstrong, R. (2019). Risk factors for Alzheimer's disease. Folia Neuropathologica, 57(2), 87-105. https://doi.org/10.5114/fn.2019.85929

Arcavi, L., & Benowitz, N. L. (2004). Cigarette Smoking and Infection. Archives of Internal Medicine, 164(20), 2206–2216.

Bai, R., Xiang-Yang Ye, J. G., Xie, Y., & Xie, T. (2022, April 5). *Oxidative stress: The core pathogenesis and mechanism of Alzheimer's disease*. Ageing Research Reviews. https://www.sciencedirect.com/science/article/abs/pii/S1568163722000617?via%3Dihub

Barrera, G., Pizzimenti, S., Daga, M., Dianzani, C., Arcaro, A., Cetrangolo, G. P., Giordano, G., Cucci, M. A., Graf, M., & Gentile, F. (2018, July 30). *Lipid peroxidation-derived aldehydes, 4-hydroxynonenal and Malondialdehyde in aging-related disorders*. Antioxidants (Basel, Switzerland). https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6115986/

Benowitz, N. L. (2009). Pharmacology of Nicotine: Addiction, Smoking-Induced Disease, and Therapeutics. Annual Review of Pharmacology and Toxicology, 49, 57–71.

Blennow, K., Dubois, B., Fagan, A. M., Lewczuk, P., de Leon, M. J., & Hampel, H. (2015). Clinical utility of cerebrospinal fluid biomarkers in the diagnosis of early Alzheimer's disease. Alzheimer's & Dementia, 11(1), 58-69.

Blinkouskaya, Y., Cacoilo, A., Gollamudi, T., Jalalian, S., & Weickenmeier, J. (2021, October 1). *Brain aging mechanisms with mechanical manifestations*. Mechanisms of Ageing and Development. https://www.sciencedirect.com/science/article/pii/S0047637421001470?via%3Dihub

Centers for Disease Control and Prevention. (2023, May 4). *Current cigarette smoking among adults in the United States*. Centers for Disease Control and Prevention. https://www.cdc.gov/tobacco/data_statistics/fact_sheets/adult_data/cig_smoking/index.htm#:~:text=In%202021%2C%20nearly%2012%20of,with%20a%20smoking%2Drelated%20disease.

Centers for Disease Control and Prevention (CDC). (2021a). Smoking & Tobacco Use: Fast Facts. https://www.cdc.gov/tobacco/data_statistics/fact_sheets/fast_facts/index.htm

Centers for Disease Control and Prevention (CDC). (2021b). Current Cigarette Smoking Among Adults in the United States. https://www.cdc.gov/tobacco/data_statistics/fact_sheets/adult_data/cig_smoking/index.htm

Chen, Z., & Zhong, C. (2014, March 24). *Oxidative stress in Alzheimer's disease - Neuroscience Bulletin*. SpringerLink. https://link.springer.com/article/10.1007/s12264-013-1423-y

Chiolero, A., Faeh, D., Paccaud, F., & Cornuz, J. (2008). Consequences of smoking for body weight, body fat distribution, and insulin resistance. American Journal of Clinical Nutrition, 87(4), 801–809.

Cornelius, M. E., Loretan, C. G., Jamal, A., Davis Lynn, B. C., Mayer, M., Alcantara, I. C., & Neff, L. (2023). Tobacco Product Use Among Adults - United States, 2021. *MMWR. Morbidity and mortality weekly report*, *72*(18), 475–483. https://doi.org/10.15585/mmwr.mm7218a1

Crimmins EM. Lifespan and Healthspan: Past, Present, and Promise. Gerontologist. 2015 Dec;55(6):901-11. doi: 10.1093/geront/gnv130. Epub 2015 Nov 10. PMID: 26561272; PMCID: PMC4861644.

De-Paula, V. J., Radanovic, M., Diniz, B. S., & Forlenza, O. V. (2019). Neurobiology of behavior disturbances in Alzheimer's disease: current status and future perspectives. Alzheimer's & Dementia, 15

Durazzo, T., Mattsson, N., & Weiner, M. (2014, June 10). *Smoking and increased Alzheimer's disease risk: A review of potential mechanisms*. Alzheimer's & Dementia. https://www.sciencedirect.com/science/article/pii/S155252601400137X?via%3Dihub

Durazzo, T. C., Meyerhoff, D. J., & Nixon, S. J. (2014). Chronic cigarette smoking: implications for neurocognition and brain neurobiology. The International Journal of Environmental Research and Public Health, 11(11), 11605–11626.

Eratne, D., Loi, S. M., Farrand, S., Kelso, W., Velakoulis, D., & Looi, J. C. (2018). *Alzheimer's disease: clinical update on epidemiology, pathophysiology and diagnosis. Australasian Psychiatry, 26(4), 347–357.* doi:10.1177/1039856218762308

Ezzati, M., Lopez, A. D., & Rodgers, A. A. (2003). Comparative Quantification of Health Risks: Global and Regional Burden of Disease Attributable to Selected Major Risk Factors. World Health Organization.

Grossman, M., Farmer, J., Leight, S., Work, M., Moore, P., Van Deerlin, V., ... & Trojanowski, J. Q. (2017). Cerebrospinal fluid profile in frontotemporal dementia and Alzheimer's disease. Annals of Neurology, 24(3), 407-411.

Imbimbo, B. P., Lombard, J., & Pomara, N. (2005). *Pathophysiology of Alzheimer's Disease. Neuroimaging Clinics of North America, 15(4), 727–753.* doi:10.1016/j.nic.2005.09.009

Ionescu-Tucker, A., & Cotman, C. (2021, July). *Emerging roles of oxidative stress in Brain aging and alzheimer's disease*. Neurobiology of aging. https://pubmed.ncbi.nlm.nih.gov/34416493/

Jamal, A., Phillips, E., Gentzke, A. S., Homa, D. M., Babb, S. D., King, B. A., & Neff, L. J. (2018). Current Cigarette Smoking Among Adults — United States, 2016. MMWR. Morbidity and Mortality Weekly Report, 67(2), 53–59.

Jha, P., Ramasundarahettige, C., Landsman, V., Rostron, B., Thun, M., Anderson, R. N., … Peto, R. (2014). 21st-Century Hazards of Smoking and Benefits of Cessation in the United States. New England Journal of Medicine, 370(4), 341–350.

Kuhn, S., Gallinat, J., & Musso, F. (2010). Smoking influences grey matter volume in the mesolimbic brain. European Archives of Psychiatry and Clinical Neuroscience, 260(2), 343–347.

Mishra, S., & Chaudhry, A. (2020). Impact of Oxidative Stress on Alzheimer's Disease Pathogenesis: Role of Metal Toxicity. Alzheimer's Disease: Pathogenesis, Cellular Mechanisms, and Therapeutics, 151–175.

Onojighofia Tobore, T. (2019). *On the Etiopathogenesis and Pathophysiology of Alzheimer's Disease: A Comprehensive Theoretical Review. Journal of Alzheimer's Disease, 1–21.* doi:10.3233/jad-181052

Ozguner, F., Koyu, A., & Cesur, G. (2005). Active smoking causes oxidative stress and decreases blood melatonin levels. *Toxicology and industrial health*, *21*(1-2), 21–26. https://doi.org/10.1191/0748233705th211oa

Patra, J., Bhatia, M., Suraweera, W., Morris, S. K., Patra, C., Gupta, P. C., & Jha, P. (2018). Exposure to second-hand smoke and the risk of tuberculosis in children and adults: a systematic review and meta-analysis of 18 observational studies. PLoS Medicine, 15(6), e1002597.

Petersen, R. C., Caracciolo, B., Brayne, C., Gauthier, S., Jelic, V., & Fratiglioni, L. (2014). Mild cognitive impairment: a concept in evolution. Journal of Internal Medicine, 275(3), 214-228.

Picciotto, M. R., & Kenny, P. J. (2013). Molecular Mechanisms Underlying Behaviors Related to Nicotine Addiction. Cold Spring Harbor Perspectives in Medicine, 3(1), a012112.

Pike, C. (2016, November 7). *Sex and the development of Alzheimer's Disease - Wiley Online Library*. Wiley Online Library. https://onlinelibrary.wiley.com/doi/pdf/10.1002/jnr.23827

Raber J, Wong D, Buttini M, Orth M, Bellosta S, Pitas RE, Mahley RW, Mucke L. Isoform-specific effects of human apolipoprotein E on brain function revealed in ApoE knockout mice: increased susceptibility of females. Proc Natl Acad Sci U S A. 1998 Sep 1;95(18):10914-9. doi: 10.1073/pnas.95.18.10914. PMID: 9724804; PMCID: PMC27995.

Salmon, T. B., Evert, B. A., Song, B., & Doetsch, P. W. (2004). Biological consequences of oxidative stress-induced DNA damage in Saccharomyces cerevisiae. *Nucleic acids research*, *32*(12), 3712–3723. https://doi.org/10.1093/nar/gkh696

Schoenborn, C. A., & Gindi, R. M. (2019). Electronic Cigarette Use Among Adults: United States, 2014–2018. NCHS Data Brief, (365), 1–8.

Shields, H. J., Traa, A., & Van Raamsdonk, J. M. (2021, February 11). *Beneficial and detrimental effects of reactive oxygen species on lifespan: A comprehensive review of comparative and experimental studies*. Frontiers in cell and developmental biology. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7905231/#:~:text=Reactive%20oxygen%20species%20(ROS)%20can,of%20guanine%20to%208%2Doxoguanine.

Sies, H. (2015, January 2). *Oxidative stress: a concept in redox biology and medicine*. Redox Biology. https://www.sciencedirect.com/science/article/pii/S2213231715000038?via%3Dihub

Shin J. H. (2022). Dementia Epidemiology Fact Sheet 2022. *Annals of rehabilitation medicine*, *46*(2), 53–59. https://doi.org/10.5535/arm.22027

Srivastava, S., Ahmad, R., & Share, S. K. (2021, February 23). *Alzheimer's disease and its treatment by different approaches: A review*. European Journal of Medicinal Chemistry. https://www.sciencedirect.com/science/article/abs/pii/S0223523421001690?via%3Dihub

Thun, M. J., Carter, B. D., Feskanich, D., Freedman, N. D., Prentice, R., Lopez, A. D., Hartge, P., Gapstur, S. M. (2013). 50-Year Trends in Smoking-Related Mortality in the United States. New England Journal of Medicine, 368(4), 351–364.

United States Department of Health and Human Services. (2020). Smoking

U.S. Department of Health and Human Services. (2014). The Health Consequences of Smoking—50 Years of Progress: A Report of the Surgeon General. https://www.ncbi.nlm.nih.gov/books/NBK179276/

Vogel, J. W., Varga, D., Schiff, N. D., Gomperts, S. N., & Fowler, K. S. (2020). Multimodal signatures of brain structure and function preceding and following advanced age. Brain Imaging and Behavior, 14(3), 767-779.

Volkow, N. D., Wang, G. J., Fowler, J. S., Logan, J., Gatley, S. J., Hitzemann, R., ... & Pappas, N. (2010). Decreases in dopamine receptors but not in dopamine transporters in alcoholics. Alcoholism: Clinical and Experimental Research, 24(11), 1575-1582.

Wills, T. A., & Sargent, J. D. (2020). The Unfinished Business of Youth Smoking Prevention. JAMA Pediatrics, 174(2), 115-116.