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Particulate Matter ($PM_{2.5}$) Air Pollution and Alzheimer's Disease: A Systematic Literature Review

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Abstract

Alzheimer's disease is currently the 6th leading cause of mortality in the United States. There is no single cause of Alzheimer's disease, however researchers have identified multiple factors including lifestyle, genetics, and environmental exposures that increase the risk for developing Alzheimer's disease. One such environmental risk factor is exposure to Particulate Matter less than 2.5 micrometer in diameter ($PM_{2.5}$). $PM_{2.5}$ is made up of metal and chemical components that become suspended in the air and when inhaled, may cause adverse health outcomes such as cancer, cardiovascular, and inflammatory diseases. The main purpose of this study was to conduct a systematic review of existing literature in order to determine the association between $PM_{2.5}$ exposure and the risk of developing Alzheimer's disease. The specific aims of the study were to determine if exposure to $PM_{2.5}$ increases the risk of developing Aβ deposits as well as neurofibrillary tau protein tangles associated with Alzheimer's disease pathology. Several databases were searched for peer-reviewed articles and a total of four eligible studies that met all of the inclusion and exclusion criteria were included in this study. The studies found that exposure and co-exposure to $PM_{2.5}$ was associated with increased development of Aβ accumulation and expression of inflammatory biomarkers in animals. Additional research studies are recommended to show cause and effect relationship between $PM_{2.5}$ exposure and Alzheimer's disease in humans.

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List of Tables and Figures

Table of Contents

Chapter One

Introduction

Alzheimer's disease (AD) is currently ranked as the 6th leading cause of mortality in the United States, however researchers estimate that Alzheimer's disease may rank 3rd following cancer and heart disease (National Institute on Aging, 2019; U.S. Department of Health & Human Services, Office of Disease Prevention & Health Promotion [HHS ODPHP], 2019). As of 2019, 5.8 million people in the United States are diagnosed with AD, but the number of cases is projected to grow to an estimated 14 million by 2050, barring advancement in successful treatment outcomes (Alzheimer's Association, 2015). Given that the only treatments available now are those that slow down the progression while providing symptomatic relief, AD is the only top listed cause of death that cannot yet be prevented or cured (Kumar, Singh, & Ekavali, 2015). While the exact cause of AD has not been confirmed, exposure to environmental factors is one of the many theories proposed (Armstrong, 2013). According to Healthy People 2020, maintaining a healthy environment by increasing the quality of air, reducing hazardous waste, and monitoring climate change is essential to maximizing quality of life and years of life (HHS ODPHP, 2019). The release of metal and chemical pollutants come from a variety of sources, but can become suspended in the air and cause poor air quality (Alzheimer's Association, 2019). The American Lung Association estimates that approximately 135 million people in the United States are at risk of developing diseases and/or experiencing premature deaths linked to poor air quality in communities with unhealthy pollution levels (American Lung Association, 2018). Studies evaluating exposure to particulate matter 2.5 ($PM_{2.5}$) and AD has gained the interest of researchers as more evidence suggests accelerated ageism, neurological damage and increased risk of developing AD pathology as well as other forms of dementia to be linked. With

suggestive evidence, additional cases of AD can be expected to grow within the years coming due to exposure to $PM_{2.5}$ pollution, especially in highly polluted areas (Huat et al., 2019). That is why it is there is a need to conduct a systematic review of existing literature in order to assess the association between $PM_{2.5}$ exposure and the risk of developing Alzheimer's disease pathology.

Background

Alzheimer's Disease

Alzheimer's disease (AD) is an irreversible neurodegenerative disease predominantly diagnosed in older adults in which dementia symptoms worsen over time due to progressive brain abnormalities (Mayo Clinic, 2017; Alzheimer's Association, 2017). Strongly suspected causes for the development of AD include poor diet, lack of physical activity, gender, history of head trauma, pre-existing conditions, environmental exposures and education level (Moulton, & Yang, 2012). However, theories most likely considered are organized into several categories including, but not limited to accelerated ageism, the degeneration of neuro-pathways, genetics and genetic factors, dysfunctional immune system, infectious agents and numerous environmental factors such as exposure to metal and chemical toxins (Armstrong, 2013; Huat et al., 2019).

There are 3 stages of AD currently identified in which symptoms vary from mild to severe known as preclinical, mild cognitive impairment, and dementia due to AD (Alzheimer's Association, 2019). While the preclinical stage is still being heavily researched, changes in cerebrospinal fluid and blood in the brain are identified. Classical hallmarks of AD develop in the mild cognitive impairment stage as well as a decline in cognition that's greater than typical age-related cognitive changes. In the final stage memory, thinking and behavioral impairment affects a the ability to carry out daily life activities, requiring assistance and noticeable AD-

related changes in the brain are present. The presence of two classical hallmarks of AD are used to clinically diagnose patients which include an accumulation of amyloid-βeta (Aβ) plaques and neurofibrillary tau protein tangles (NFT) at an accelerated rate (Alzheimer's Association, 2015; Block, & Calderón- Garcidueñas, 2009). Aβ plaques are formed under an abnormal process in which beta secretase (BACE) and gamma secretase enzymes assist in breaking down amyloid precursor protein (APP) clipping off larger than normal fragments of sticky, insoluble beta amyloid (Aβ) (Alzheimer's Association, 2019; Selkoe, 2001). Aβ accumulates between neurons and along neuronal pathways accumulating into plaques that form into Aβ plaques. This causes a decline in the ability of neurons to communicate and electronically signal throughout the brain. A natural immune, or an inflammatory response is activated inducing oxidation (oxidative stress) in which more free radicals are produced than what the body can handle, resulting in the progression, production and pathogenesis of AD pathology (Butterfield, Swomley, & Sultana, 2013). This results in an increase of damaged cells and tissues as well as developed mutations, impairment of DNA and a mass loss of healthy neurons (Khansari, Shakiba, & Mahmoudi, 2009). Although less understood compared to Aβ, it is suspected that the overproduction of oxidative stress plays a crucial role in the induction of primary hallmark neurofibrillary tangles (NFT) (Butterfield, Swomley, & Sultana, 2013; Liu et al., 2015).

Tau proteins located in the central nervous system aids in the stabilization of microtubules, promoting microtubule assembly in order to successfully transfer nutrients within (Mietelska-Porowska, Wasik, Goras, Filipek, & Niewiadomska, 2014). As observed in AD, a disruption in the hyperphosphorylation of tau causes the proteins to unbind from microtubules and clump into insoluble tangles and into filaments over time. When NFT's are formed,

neurons can no longer signal messages properly and apoptosis, programmed cell death, initiates. Physical changes in the brain such as atrophy (shrinking), narrowing of ridges in the brain, widening of grooves in the brain and the enlargement of brain ventricles begin to form (National Institute on Aging, 2017).

Particulate Matter 2.5 ($PM_{2.5}$)

Particulate matter 2.5 ($PM_{2.5}$) is a combination of solid and liquid droplets that either come from a direct source or are the product of a chain reaction formed in the atmosphere (Fortoul et al., 2015). $PM_{2.5}$ are characterized as particles with diameters of 2.5 or smaller and are known as fine or inhalable particles (U.S. Environmental Protection Agency [EPA], 2018). Ambient sources of $PM_{2.5}$ include emissions from construction sites, power plants, traffic exhausts and burning fuels that can last in the atmosphere for up to days (Kim, Kabir, & Kabir, 2015; Fortoul et al., 2015). Indoor sources of $PM_{2.5}$ include particles that come from cooking, wood combustion, candle burning, furnace burning and even tobacco smoking (National Academies of Sciences, Engineering, & Medicine, 2016). Many of these sources are considered as anthropogenic while others derive from natural sources such as sea salt, soil particles, forest fires, ash from volcanoes and pollen (Fortoul et al., 2015). $PM_{2.5}$ is made up of many components, one being metal, that adhere to particles and its surfaces. These metal particles can be emitted from industrial activities, combustion, non-exhaust emissions, or impurities from fuel additives. National standards and regulations are mandated in the United States to control the amount of pollutants emitted into the atmosphere.

There are various standards and regulations for environmental air pollution in the United States. To protect environmental and human health, the environmental protection agency (EPA) has promulgated the National Ambient Air Quality Standards (NAAQS) for six criteria air

pollutants that includes $PM_{2.5}$ (EPA, 2018). The EPA has set both the primary and secondary standards for $PM_{2.5}$ (annual mean, averaged over 3 years) and these include the one year primary standard of 12.0 $\mu g/m^3$, the one year secondary standard of 15.0 $\mu g/m^3$and the 24-hour primary and secondary standard of 35 $\mu g/m^3$ (as 98th percentile, averaged over 3 years) (Weinhold, 2013). The primary standards are set to protect public health, including the health of "sensitive" populations such as asthmatics, children, and the elderly. In addition, secondary standards are set to protect public welfare, including protection against decreased visibility and damage to animals, crops, vegetation, and buildings (Mcrae, 2017).

Air quality levels for $PM_{2.5}$ have declined by as much as 50% when compared to 20 years ago, limiting the amount of particles emitted into the air (University of Southern California Environmental Health Centers, 2015). However, current regulatory mandates do not guarantee sufficient air quality as well as a reduction in adverse health effects associated with exposure. Over 20 million people in the United States is estimated to live in areas in which $PM_{2.5}$ concentration levels exceed the EPA standard annually for both short and long-term exposure (Kilian, & Kitazawa, 2018), putting people at risk of developing adverse health diseases and possibly AD. Previous research has confirmed that $PM_{2.5}$ exposure is linked to the development of serious health conditions and diseases including cancer/s, cardiovascular issues, and inflammatory diseases (Uttara, Singh, Zamboni, & Mahajan, 2009; Huang, Pan, Wu, Chen, & Chen, 2017; Du, Xu, Chu, Guo, & Wang, 2016). More recently have studies suggested that exposure to both short and long term $PM_{2.5}$ in human and animal subjects to be linked to the development of AD. Hypothesized, $PM_{2.5}$ exposure induces an inflammatory stress and oxidative stress response in the central nervous system that can lead to AD-like symptoms and pathology (Power, Adar, Yanosky, & Weuve, 2016; Bhatt, Puig, Gorr, Wold, & Combs, 2015; Ljubimova

et al., 2018).

Literature Review

Metal components associated with $PM_{2.5}$ contribute to less than 1% of the $PM_{2.5}$ mass, however are recognized as the most important due to the evidence linked to adverse health outcomes (Jun-Wei et al., 2019). Metal components can come from numerous sources and depending on the source can also depend on their toxic potency. Jun-Wei et al. (2019) acknowledge several trace metals associated with sources of $PM_{2.5}$. Trace metals including magnesium (Mg) and calcium (Ca) can derive from natural sources such as sea salt aerosol and biomass. Trace metals including nickel (Ni) can derive from industrial activities, such as from oil combustion, as well as arsenic (As) and lead (Pb) from coal combustion. Additional trace metals can derive from both natural and anthropogenic sources such as potassium (K) from either wood burning or biomass, and crustal elements such as silicon, calcium (Ca), aluminum (Au), zinc (Zn), cobalt (Co) and iron (Fe) from both natural and anthropogenic dust. Metal components can range in surface concentration levels, however researchers suggest that the concentration levels and associated effects are significantly underestimated due to a bias interpretation and an underestimation of industrial emissions (Hutzell, & LueckenFate, 2008; Dore et al., 2014). Depending on the portal of entry, the deposition of matter and the toxic potency of $PM_{2.5}$, inflammation stress and oxidative stress responses will differ (Liu et al., 2017).

There are two portals of entry recognized in which $PM_{2.5}$ can enter the body and reach the brain in order to cause an effect (Block, & Calderón-Garcidueñas, 2009). One, via systemic in which $PM_{2.5}$ particles deposited in the alveolar area in the lungs translocate through the systemic circulation system, and to extra pulmonary organs such as the brain by crossing the blood brain barriers. Two, via the olfactory route in which $PM_{2.5}$ particles travel along the olfactory pathway

in a gradient fashion through the olfactory mucosa, olfactory bulb, and frontal cortex by successfully translocating across epithelial barriers (Bandyopadhyay, 2016; Block, & Calderón-Garcidueñas, 2009). This fashion has been confirmed by Calderon- Garciduenas et al. (2003) after traces of nickel (Ni) was identified along and throughout the olfactory pathway. When $PM_{2.5}$ particles enter either portal this causes a disruption of homeostasis, which induces an inflammatory response (Cheignon et al., 2018). However, researchers have taken more interest in the olfactory route due to existing evidence. According to Lachen-Montes et al. (2019), olfactory dysfunction is present in 90% of AD cases before other regions of the brain are affected by the course of the disease. Existing research also confirms that heavy metals associated with criteria air pollutants, such as $PM_{2.5}$, leads to the decline of olfactory dysfunction due to the anatomic position and susceptibility of the olfactory nerve (Ajmani, Suh, & Pinto, 2016). This evidence suggests that the inhalation of $PM_{2.5}$ may be linked etiologically to neuropathology.

The two biological mechanisms that are associated with $PM_{2.5}$-pollution induced neuropathology are referred to as inflammation stress and oxidative stress (Bandyopadhyay, 2016). Toxic components, such as metal, associated with $PM_{2.5}$ are scientifically recognized as a catalyst because metal particles are more prone to oxidative stress as compared to other elements and induce neurodegenerative pathology through inflammatory mechanisms (Cheignon et al., 2018). As a result of a catalyst effect, the over production of reactive oxidative species (ROS) not only enhances the upregulation of enzymes that assist in breaking down APP (Muche, Arendt, & Schliebs, 2017), but damages the Aβ peptide when they bind together as well as DNA, fatty tissues and proteins in the brain. The accumulation of damaged Aβ leads to plaque formation in the cortex and hippocampus areas of the brain (Liu, Young, Chen, Kaufman, & Chen, 2016). Metal components associated with $PM_{2.5}$ are also recognized as a pro-inflammatory

stimulus to the body, a high risk factor for neurodegenerative diseases (Block, & Calderón-Garcidueñas, 2009). In an orchestrated response, a range of toxic inflammatory biomarkers are activated or expressed in order to produce a synergistic neurotoxicity effect (Metcalfe, & Figueiredo-Pereira, 2010). Brenner et al. (2015) details a list of inflammatory biomarkers associated with inflammatory responses including, but not limited to interleukin alpha (IL-1α), interleukin beta (IL-1β), interleukin-2 (IL-2), interleukin-6 (IL-6), interleukin-8 (IL-8), interleukin-12 (IL-12), tumor necrosis factor alpha (TNF-α), interferon gamma (IFN-γ), white cell count, nuclear factor kappa-light-chain-enhancer (NF-kB), cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2), ROS, serum amyloid A, and c-reactive protein. The abnormal expression of inflammatory biomarkers causes neuronal damage, disrupts the phosphoralization of tau proteins leading to the nuerodegeneration of microtubule pathways preceding tau tangle formation. This evidence suggests that $PM_{2.5}$ may be capable of inducing a series of biological effects that causes neurodegeneration and AD pathology. However, it is important to analyze the effects of co-exposure as $PM_{2.5}$ and additional criteria air pollutants co-exist in the air and can cause harm to human health and the environment.

Gaseous pollutants, such as sulfur dioxide (SO_2), ozone (O_3) and nitrogen dioxide (NO_2), are some of the precursors associated with the formation of $PM_{2.5}$ pollutants and co-exist in the air putting sensitive populations at a higher risk of developing adverse health outcomes (Ku, Ji, Zhang, Li, & Sang, 2016). In order to gain knowledge on the effects of co-exposure to $PM_{2.5}$ and gaseous pollutants on the development of AD pathology, Zarandi, Shahsavani, Khodagholi, and Fakhri (2016) carried out an experimental study. Rodent subjects were randomly divided into three groups including $PM_{2.5} + SO_2 + NO_2 + O_3$, $SO_2 + NO_2 + O_3$, and a control group

without exposure. Rodents were exposed for three hours a day, four days a week for three months to an average concentration of 37.76 ± 11.96 μm/m^3 of $PM_{2.5}$, 5.90 ± 130 ppb of SO_2, 16.55 ± 2.30 ppb of O_3 and 56.88 ± 7.82 ppb of NO_2. Researchers identified traces of metal including aluminum (Al), calcium (Ca), copper (Cu), sodium (Na), iron (Fe), nickel (Ni) and lead (Pb) in the sample collection. Using an enzyme-linked immunosorbent assay (ELISA) technique to measure Aβ levels in the brain after exposure treatment, results showed that co-exposure to $PM_{2.5}$ + SO_2 + NO_2 + O_3 lead to a significant increase of Aβ protein levels in the hippocampus region in the brain. However, exposure to SO_2 + NO_2 + O_3 without $PM_{2.5}$ did not affect Aβ protein levels in the brain. Co-exposure to $PM_{2.5}$ and additional criteria pollutants may be associated with an increased risk of developing AD pathology as they can produce a greater effect of synergistic toxicity.

With this evidence, $PM_{2.5}$ pollution may be associated with the development of AD pathology. A source-effect relationship has not yet been scientifically confirmed between $PM_{2.5}$ exposure and AD due to a variety of reasons including a lack of understanding of AD causation, the molecular mechanisms behind PM aggravating disease progression, and defining and replicating individual sources of $PM_{2.5}$ exposure (Killin, Starr, Shiue, & Russ, 2016; Kim, Kabir, & Kabir, 2015; Kim, Lee, Choi, Kim, & Cho, 2015; Kumar, Singh, & Ekavali, 2015). Therefore, $PM_{2.5}$ exposure and its association with AD should be examined further.

Objective

The main objective of this study is to conduct a systematic review of existing literature and determine the association between $PM_{2.5}$ exposure and the risk of developing AD pathology. The specific aims of the study are as follows:

Aim #1: To determine if exposure to PM2.5 increases the risk of developing Alzheimer's disease primary hallmark Aβ deposits

Aim #2: To determine if exposure to $PM_{2.5}$ increases the risk of developing Alzheimer's disease primary hallmark neurofibrillary tau protein tangles

Chapter Two

Methods

Search Strategy and Selection Criteria

A systematic literature review of current research on $PM_{2.5}$ air pollution and AD was conducted in accordance with existing protocol developed by Moher et al. (2009). This was based on clearly defined inclusion and exclusion criteria as well as the application of search strategies of various databases to ensure efficient selection and retrieval of relevant published articles.

Databases used to search peer-reviewed articles included Pubmed, ScienceDirect, and Google Scholar. The search involved the use of existing search strategy in combination with key phrases "Alzheimer's disease" or "Alzheimer's disease pathology" or "Alzheimer's disease hallmarks" or "Alzheimer's disease biomarkers" or "particulate matter pollution" or "$PM_{2.5}$ exposure" or "$PM_{2.5}$ pollution" or "fine particulate matter."

Inclusion Criteria

Eligible populations included in this search were humans and mammals of any and all ages. Subjects of studies must have been cleared of all pre-existing health conditions as well as any symptoms exhibiting serious illnesses or diseases. Full text articles must have been available online for full review. Studies published between January 1995 to July 2019 in the United States and in the English language were considered eligible for inclusion. Studies performed in any country outside of the United States, but were reported in English were also considered. Titles of articles were to include at least one key term from the key phrases used to perform the initial search in order to be considered for abstract review. When reviewing abstracts, variables "Alzheimer's disease" and "particulate matter" must have been indicated as the focus variables of

the study. In addition, a discussion of AD-related pathological effects observed by researchers after $PM_{2.5}$ exposure must have been identified. Key-like terms were used to consider studies for further eligibility while reviewing abstracts included inflammation, oxidative stress, tau tangles or disconnections, neurodegeneration, impaired pathways, declining cognition, Aβ and hallmarks or markers. During the final screening process, the concentration level of $PM_{2.5}$ and exposure time period must have been clearly defined. Results must have evaluated the specific aim of #1: determining if exposure to $PM_{2.5}$ increases the risk of developing Alzheimer's disease primary hallmark Aβ deposits and/or specific aim #2: determining if exposure to $PM_{2.5}$ increases the risk of developing Alzheimer's disease primary hallmark neurofibrillary tau protein tangles after $PM_{2.5}$ exposure.

Exclusion Criteria

Full-text studies unavailable online or published prior to 1995 were the first to be excluded. All studies that were conducted on $PM_{2.5}$ and AD, but were published in any language other than English or were transcribed to English were excluded. If one or more of the initial key vocabulary terms or key-like terms were not included the title description, studies were not considered for review. If abstracts did not include a discussion of AD-related pathological effects after $PM_{2.5}$ exposure using key-like terms, studies were excluded for final review. When screening the final selection of studies, those that that did not evaluate for or meet the specific aim #1 or #2 were not included in the final study results. Studies that did not disclose the concentration level of $PM_{2.5}$ in which cases were exposed to or detail exposure period were not eligible. Duplicates were excluded.

Data Analysis

This systematic review was conducted to determine if exposure to $PM_{2.5}$ was associated

with the formation of Aβ plaques. $PM_{2.5}$ exposure levels reported in the studies were expressed in concentrations of $\mu g/m^3$over a certain period of time.

In addition, this review determined if $PM_{2.5}$ exposure was associated with the activation of inflammatory biomarkers. Inflammatory biomarkers are proteins or enzymes that are produced or expressed in response to an injury or an underlying disease and are commonly measured in the laboratory using an ELISA kit or immunostaining technique.

Furthermore, this review will determine if co-exposure to $PM_{2.5}$ and other pollutants was associated with the formation of Aβ plaques and the activation of inflammatory markers. Co-exposure refers to a multi-pollutant mixture in which subjects were exposed to. Subjects were co-exposed to a defined concentration level of pollutants throughout the entire exposure period.

The selection of studies included in this review was in accordance with the existing protocol developed by Moher et al. (2009). An initial search using key phrases yielded a total of 32,111 studies, including 29,518 articles from Pubmed, 2,300 articles from ScienceDirect, and 299 articles from Google Scholar. A total of 1,661 full-text studies that were either unavailable online or were published in a language other than English or prior to 1995 were excluded. After exclusion, 30,456 studies remained for title inclusion review. Titles of 654 studies that met the exclusion criteria were further screened for abstract, title, and inclusion criteria. After further review, 102 studies met all title and abstract inclusion data criteria and remained to be reviewed in the final screening process in order to assess if they met all inclusion criteria. Studies excluded for not meeting all inclusion criteria included a total of 58 articles. Also, 40 studies were excluded because they were duplicates. A total of 4 studies remained eligible to be included in this systematic review. Studies were categorized into various themes as follows:

(1) Aβ plaques

(2) Inflammatory biomarkers

(3) Co-exposure

Chapter Three

Results

Table 1 provides an overview of the final 4 studies included in this review. Of the four studies conducted on experimental animals, three studies (Jang et al., 2018; Lui et al., 2017; Yang, Cheng, Zhang, Li, & Dong, 2017) were conducted outside of the United States and one study (Bhatt, Puig, Gorr, Wold, & Combs, 2015) was conducted in the United States. All procedures used in the studies were in accordance with the National Research Council of the National Academies Guide for the Care and Use of Laboratory Animals and were approved by their various Institutional Review Boards prior to conducting the experimental studies.

Table 1: An Overview of Studies (n=4) included in the Review

Year	Author(s)	Title	Objective	Results	Conclusion
2018	Jang et al.	Particulate matter activated glial cells and increased beta-amyloid in hippocampal tissues of transgenic Alzheimer's mouse: Involvement of PARP-1	To investigate the pathogenic mechanisms associated with fine particulate matter and examine if fine particulate matter directly affects Aβ levels.	Fine particulate matter was observed to activate PARP-1 in neuronal cells, induce glial activation and increase Aβ levels in hippocampal tissues.	Fine particulate matter activates PARP-1, increasing Aβ levels and activated glial cells (inflammatory biomarker) in the hippocampal tissues of mice.

Year	Author(s)	Title	Objective	Results	Conclusion
2017	Yang, Cheng, Zhang, Li, & Dong	The role of pro-/anti-inflammation imbalance in Aβ42 accumulation of rat brain co-exposed to fine particulate matter and sulfur dioxide	To determine if there is a link between adverse effects in the brain and the exposure to SO_2 and fine particulate matter ($PM_{2.5}$).	Exposure to fine particulate matter increased Aβ in the brain cortex and hippocampus. The combined exposure to fine particulate matter and SO_2 enhanced TNF-α, IL-6 expressions and Aβ levels significantly in the 6.0 mg/kg, and 24.0 mg/kg exposure group.	Fine particulate matter affects the balance of pro-/anti-inflammatory lipid mediators, triggering abnormal expression of cytokine TNF-α mRNA in the fine particulate matter alone exposure group and TNF-α protein in the co-exposure group. Aβ levels in the cortex and hippocampus were identified as dose- dependently increased by fine particulate matter.
2015	Bhatt, Puig, Gorr, Wold, & Combs	A Pilot Study to Assess the Effects of Long-Term Inhalation of Airborne Particulate Matter on Early Alzheimer-Like Changes in the Mouse Brain	To study the effect of 3 and 9-months of air $PM_{2.5}$ exposure on brain inflammatory phenotype and pathological hallmarks of AD in mice.	A significant increase in pro-inflammatory enzymes COX-1 and COX-2, cytokine profile, and Aβ deposits were identified in the 9-month exposure group.	Chronic inhalation of airborne particulate matter promoted specifically the amyloid-associated pathology, increased BACE levels and decreased APP levels. These changes correlated with increases in COX-1 and COX-2 protein levels and a modest increase in the chemotactic cytokine profile.
2017	Liu et al.	At seeming safe concentrations, synergistic effects of $PM_{2.5}$ and formaldehyde co-exposure induces Alzheimer-like changes in mouse brain	To identify whether there are differences in the development of AD due to exposure to $PM_{2.5}$, formaldehyde or a multi-pollutant ($PM_{2.5}$ plus formaldehyde); and explore the possible mechanisms of the effects.	$PM_{2.5}$ or formaldehyde exposure alone had little to no effect on the brain, however co-exposure lead to an accumulation of Aβ and an increase of Tau-P, reactive oxidative species and COX-2 expression.	The high expression of Aβ and Tau-P lead to neuronal cell death and was induced by co- exposure. The synergistic effect of co-exposure was detected in oxidative species accumulation and reflected in the COX-2 expression.

Jang et al. (2018) used 30 μg /ml of $PM_{2.5}$ in membrane-containing wells for twenty-four hours. All samples of mice brain were randomly divided into four groups of n=6 slices each and exposed for twelve days. These groups included $PM_{2.5}$, $PM_{2.5}$ + polymerase-1 (PARP-1), PARP-1 and an ELISA was used for the laboratory analysis. The researchers observed a significant amount of increased Aβ levels in hippocampus tissues of the brain.

Yang et al. (2017) collected $PM_{2.5}$ at a local sampling site using fiber filters and exposed nine groups of six rats each via intra-tracheal installation. Three exposure groups of rats included $PM_{2.5}$ alone, SO_2 alone, and $PM_{2.5}$ + SO_2 as well as a control group with no exposures. Rats were exposed to 1.5 mg/kg, 6.0 mg/kg, and 24.0 mg/kg of their body weight to 500 μg /m^3 of $PM_{2.5}$ once every two days for ten days. Using an ELISA, the researchers identified significantly elevated amounts of Aβ deposition at a dose of 6.0 mg/kg and at 24.0 mg/ kg of $PM_{2.5}$ of the rat's body weight in both the cortex and hippocampus regions in the $PM_{2.5}$ group only.

Bhatt et al. (2015) used a concentration enrichment system known as the Ohio air pollution exposure system for interrogation of systematic effects and exposed mice to an annual average of 11.7 ± 6.1 μg /m^3 of $PM_{2.5.}$ Mice were exposed for six hours a day, five days a week for either 3-months or 9-months of exposure treatment. Using an ELISA, the researchers measured and reported a significant amount of Aβ accumulation after 9-months of exposure treatment.

In addition, Jang et al. (2018) further examined the association between $PM_{2.5}$ exposure and neuroinflammation by examining PARP-1 involvement and activation of glial cells. Using a commercial quantification kit to measure, researchers identified significant changes to nicotinamide adenine dinucleotide (NAD) levels, activation of PARP-1 in a dose-response manner and activation of glial cells identified by their morphology in mice brain samples.

Researchers confirmed that the inflammatory response was positively associated with $PM_{2.5}$ exposure treatment due to the dose-response manner observed.

Yang et al. (2017) also identified a notable increase in both TNF-α mRNA expression and TNF-α or IL-6 levels in rats who were exposed to 6.0 mg/kg and at 24.0 mg/kg per their body weight to 500 μg /m^3 of $PM_{2.5}$. When specifically examining TNF-α mRNA expression, researchers noted a significant upregulation in the cortex region. In addition, increased levels of TNF-α or IL-6 as well as a reduction in the expression of TGF-β were identified in the hippocampus region of the brain.

Bhatt et al. (2015) identified a significant increase in pro-inflammatory enzymes COX-1 and COX-2 after 9-months of exposure treatment using a western blot analysis. Researchers also identified an increase in BACE levels as well as an increase in chemotactic cytokine profile using a mouse inflammatory cytokine array. Based on this data, researchers concluded that $PM_{2.5}$ exposure alters the brain inflammatory profile of mice.

More critically, Liu et al. (2017) evaluated the effects of co-exposure on the development of AD pathology. Mice were randomly divided into four groups including $PM_{2.5}$ only, $PM_{2.5}$ + formaldehyde, formaldehyde only and control. Using recorded measurements, researchers co-exposed subjects to .193 mg/kg/day to 100 μg/m^3 of $PM_{2.5}$ and .155 mg/kg/day of formaldehyde for seven days via intra-nasal installation with a volume of 10 μg/l. Using an ELISA and immunostaining techniques, researchers identified a significant amount of Aβ accumulation present in the cerebral cortex. In addition, there was a significant increase in the expression of phosphorylated tau in the cortex, ROS production, and COX-2 expression.

Yang et al. (2017) also evaluated the effects of co-exposure on the development of AD pathology. Rats were co-exposed to 1.5 mg/kg, 6.0 mg/kg, and 24.0 mg/kg per their body weight

to 500 μg/m^3 of $PM_{2.5}$. and 5.6 mg/m^3 of SO_2 for six hours after $PM_{2.5}$ exposure. The researchers identified a significant amount of Aβ accumulation in the cortex and hippocampus regions of the brain in rats exposed to 6.0 mg/kg and at 24.0 mg/kg per their body weight. In addition, co-exposure was observed to cause an increase in the expression of TNF-α and IL-6 as well as a reduction in the expression of TGF-β in the cortex and hippocampus regions of the brain.

Results from these studies suggested that $PM_{2.5}$ exposure induced both inflammatory and oxidative stress responses in experimental animals. These responses may potentially lead to increased Aβ formation and expression of inflammatory biomarkers in the animals tested. In addition, the results suggested that co-exposure to $PM_{2.5}$ and other pollutants may exert a greater effect of neurotoxicity and significantly increase Aβ formation and expression of inflammatory markers.

Chapter Four

Discussion

Results from three of the four studies reviewed (Bhatt et al., 2015; Jang et al. (2018); Yang et al., 2017) identified increased Aβ formation in the cortex and hippocampus regions of the brain in rat and mice after $PM_{2.5}$ exposure alone. These studies showed that some metal components associated with $PM_{2.5}$ induced a catalyst effect under oxidative stress (Cheignon et al., 2018). Oxidative stress responses were reported by Muche et al. (2017) to enhance the upregulation of BACE enzymes. In the natural course of AD, BACE and gamma secretase are responsible for the breakdown of APP that clip off large fragments of sticky, insoluble Aβ that accumulate into plaques (Alzheimer's Association, 2019; Selkoe, 2001). The study Bhatt et al. (2015) showed increased BACE levels and decreased full length APP after 9-months of exposure treatment of mice. The authors demonstrated that exposure to $PM_{2.5}$ correlated with an increased accumulation of Aβ fragment. However, as a result of a catalyst effect, the over production of ROS not only enhanced the upregulation of BACE that enhanced the cutting of APP (Muche et al., 2017), but also damaged the Aβ peptide and the surrounding DNA, fatty tissues and proteins (Cheignon et al., 2018). The accumulation of Aβ leads to plaque formation in the cortex and hippocampus areas of the brain (Liu, Young, Chen, Kaufman, & Chen, 2016).

Furthermore, results from Bhatt et al. (2015), Jang et al. (2018), and Yang et al. (2017) identified an increase of inflammatory biomarker expression after exposure to $PM_{2.5}$. Metal components associated with $PM_{2.5}$ are considered as an inflammatory stimulus to the body, a high risk for AD (Block & Calderón-Garcidueñas, 2009). When fine particles deposit in the body, an inflammatory response activates and toxic inflammatory biomarkers are expressed (Metcalfe, & Figueiredo-Pereira, 2010). TNF-α is a pro-inflammatory biomarker that is found to

be significantly elevated in AD patients. Observed in Yang et al. (2017), researchers reported a reduction in the expression of TGF-β as well as an increase of TNF-α and IL-6. This data demonstrated to researchers that the increase expression of TNF-α and IL-6 levels induced the reduction of TGF-β. This reduced expression is hypothesized by researchers to be a neuro-protection mechanism response as a result of $PM_{2.5}$ exposure. In addition, elevated COX-2 expression in neurons in the hippocampus region of the brain is present in AD patients as well. Bhatt et al. (2015) were able to identify an increase in COX-1 and COX-2 expression, both proteins that were observed to have key roles in the development of $PM_{2.5}$-induced AD pathology in the brain of mice after 9-months of exposure treatment.

Moreover, results from Liu et al. (2017) and Yang et al. (2017) identified an increase of Aβ and expression of inflammatory biomarker expression after co-exposure. As hypothesized by Zarandi, Shahsavani, Khodagholi, and Fakhri (2019), co-exposure to multiple pollutants may increase the risk of developing AD pathology due to the inflammatory response producing a greater effect of synergistic toxicity. Yang et al. (2017) observed a significantly higher amount of Aβ accumulation and TNF-α mRNA expression after co-exposure to $PM_{2.5}$ + SO_2 compared to $PM_{2.5}$ exposure alone in the brain of rats. Researchers believed that the combination of co-exposure had exert a greater effect of neurotoxicity. Furthermore, the increase of Aβ was found to be positively correlated to the expression of inflammatory biomarkers TNF-α, IL-6 and the TNF-α/TGF-β1 ratio. This data demonstrated to researchers that co-exposure to $PM_{2.5}$ and SO_2 induced AD pathology and that inflammatory biomarkers played an important role in the development. Liu et al. (2017) found a similar association as researchers observed an increase in Aβ induced by co-exposure to $PM_{2.5}$ and formaldehyde in mouse brain. In addition, researchers detected a high accumulation of ROS believed to be responsible for inducing inflammation and

damaging cells resulting in the occurrence of disease pathology. Liu et al. (2017) concluded that a greater synergistic effect was induced by co-exposure which was detected by the amount of ROS accumulation and reflected in the expression of COX-2.

Although researchers Bhatt et al. (2015), Jang et al. (2018), Liu et al. (2017) and Yang et al. (2017) concluded that a positive association existed between $PM_{2.5}$ exposure and co-exposure to Aβ formation and inflammatory biomarker expression, research cannot confirm that $PM_{2.5}$ causes AD. As previously mentioned, a lack of understanding of AD causation is one of the main reasons why causation between $PM_{2.5}$ and AD cannot be confirmed (Killin et al., 2015; Kim et al., 2015; Kumar et al., 2015). Research has not confirmed if inflammatory mechanisms induce AD pathology or if AD pathology induces an inflammatory response (Chiroma et al., 2018). Therefore, going forward in the public health field it is imperative that more research is conducted on the causation of AD in order to confirm the association between $PM_{2.5}$ pollution exposure and co-exposure.

Study Limitations

The limitations of this study were due to a lack of published studies in humans and diversity in study samples. All eligible studies included in the final results used rodents as subjects and these were bred under very controlled ambient $PM_{2.5}$ exposure and strict conditions. This limitation could have potentially skewed the results of this study in that the results of animals cannot be generalized to humans. In addition, humans are exposed to multiple sources of $PM_{2.5}$ and other criteria pollutants in both the ambient and indoor environments. Research cannot assume that the AD-related pathology observed by researchers in rodent subjects would follow similar pathophysiological processes in human subjects. Furthermore, available published research does not dictate one cause, but rather multiple risks of exposure that may be associated

with the development of AD. Finally, social determinants of health such as physical activity, genetics, or pre-existing conditions in combination with exposure to $PM_{2.5}$ were not assessed for in any of the four studies included in this review.

Conclusion

The purpose of this capstone project was to conduct a systematic review of existing literature in order to determine the association between $PM_{2.5}$ exposure and the risk of developing AD pathology. Results of animal studies from the four articles included review suggested that the inhalation of metal components in $PM_{2.5}$ were associated with inflammatory and oxidative stress responses that may induce AD pathology. These responses have been shown to increase the accumulation of Aβ and activate inflammatory biomarkers in experimental animals and may potentially lead to the development of Aβ plaques and neurofibrillary tau tangles, the two clinical hallmarks of AD pathology. In addition, co-exposure to $PM_{2.5}$ and SO_2 may exert a greater toxicity effect and increase the risk of Aβ accumulation and expression of inflammatory biomarkers significantly. It must be noted that all four studies reviewed during this project were based on experimental animals (rodents), hence these results cannot be generalized to humans. Therefore, more research is necessary in order to prove causation between exposure to $PM_{2.5}$ air pollution and AD.

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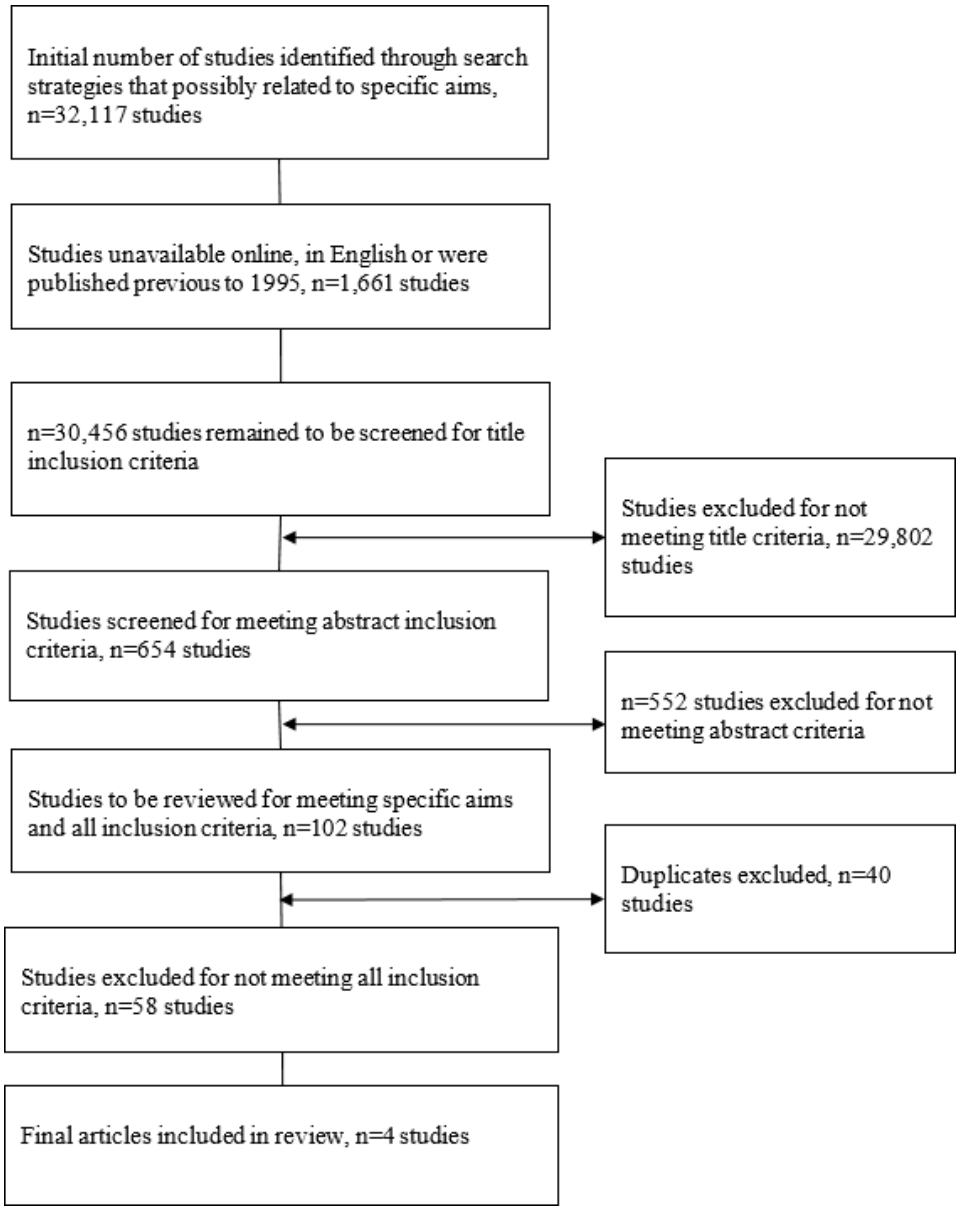
Appendix I

Figure 1: Flow chart of study selection and results as adapted from protocol by Moher et al., (2009)



Steps on the Flow Chart

1. Initial number of studies identified through search strategies that possibly related to specific aims, n=32,117 studies
2. Studies unavailable online, in English or were published previous to 1995, n=1,661 studies
3. n=30,456 studies remained to be screened for title inclusion criteria
    a. Studies excluded for not meeting title criteria, n=29,802 studies
4. Studies screened for meeting abstract inclusion criteria, n=654 studies
    a. n=552 studies excluded for not meeting abstract criteria
5. Studies to be reviewed for meeting specific aims and all inclusion criteria, n=102 studies
    a. Duplicates excluded, n=40 studies
6. Studies excluded for not meeting all inclusion criteria, n=58 studies
7. Final articles included in review, n=4 studies