Fine Particulate Matter (PM2.5) and Alzheimer's Disease: A Systematic Review of Biological Mechanisms, Public Health Implications, and Economic Burden

Abstract

Exposure to fine particulate matter (PM2.5) has been linked to neurodegenerative diseases, including Alzheimer's Disease (AD). PM2.5, which consists of airborne particles smaller than 2.5 micrometers, can penetrate the respiratory system and reach the brain, potentially triggering neuroinflammation and accelerating AD progression. This systematic review explores three aspects between the factors: the biological mechanism, the public health implications of the relationship, and the economic burden on society. A comprehensive literature search was conducted using UCSB Library and PubMed databases yielding 12 relevant studies published from 2015 onwards. Findings show that PM2.5 exposure is associated with increased amyloid-B deposits and neuroinflammation in both animals and human studies, supporting potential causal pathways for AD. Additionally, proximity to major roads correlates with higher AD risk, emphasizing the public health importance of controlling PM2.5 levels. Economic analyses from Sweden and China estimate that up to 16.5% of AD cases may be attributable to PM2.5, with significant healthcare costs per case. These findings highlight the need for further research to confirm causality and develop policies to reduce PM2.5 exposure, leading to the mitigation of AD's prevalence and its economic burden on society.

Introduction

Air pollution has been a growing topic of discussion in the 21st century. Formed by various particles both natural and chemical, air pollution is the leading factor in death of approximately 4.2 million people every year. [3] Particulate matter, being among the most toxic of the pollution particles, is a form of minute air pollution classified into three groups: coarse, fine, and ultrafine. Each is defined by their particle size, being less than 10 micrometers, less than 2.5 micrometers, and less than 100 nanometers respectively [2]. Fine particulate matter ($PM_{2.5}$) is of the most concern in the scientific community, being harmful to humans while also extremely difficult to detect. It has been shown to be directly related to the development of neurodegenerative diseases such as Alzheimer's Disease (AD) and Parkinson's [1]. Among leading research on the mechanisms between the two factors, the Amyloid Cascade Hypothesis seems most promising [12]. $PM_{2.5}$ has been shown to create excess levels of amyloid-β in the brain. The hypothesis states that the buildup of amyloid-β peptide in the brain triggers a series of pathological processes. Ultimately leading to neurodegeneration and the symptoms of cognitive decline associated with AD. In addition, $PM_{2.5}$ has been experimentally proven to cause inflammation of the olfactory bulb and hippocampus of mice. Inflammation in these areas has also been associated with the development of neurodegenerative diseases in humans. Taking these various factors into account, leads to the reasoning that exposure to $PM_{2.5}$ may be a great contributor of AD-neuropathology [4].

Growing societal concerns regarding environmental health have spurred an increase in studies on $PM_{2.5}$. Considered a relatively new field only gaining popularity in the late 2000's and early

2010's, many parts of the human body have been assessed and studies written about them. Examples being topics such as neurodegenerative diseases, lung diseases, heart diseases, and others. Notably, the relationship between $PM_{2.5}$ exposure, brain inflammation, and the development of neurodegenerative diseases has gained significant attention [7][5]. Systematic reviews summarizing the findings around neurodegenerative diseases have been formed giving a wide overview of the effects $PM_{2.5}$ has on the brain [6][9]. However, these reviews often cover broader topics, making it difficult to derive conclusive insights without a focused approach. This gap in conclusion creates the need for a systematic review centered specifically on $PM_{2.5}$'s impact on AD.

This systematic literature review adopts a focused approach similar to other reviews but narrows its scope exclusively to $PM_{2.5}$'s relationship with AD. This review serves to synthesize existing research on the connection between $PM_{2.5}$ exposure and AD development, emphasizing the biological mechanisms between the two factors. Additionally, it will focus on two topics including the correlational factors present and the economic burden caused by the relationship between $PM_{2.5}$ and AD.

Methodology

The following systematic literature review was carried out using the process described in class [13]. The process contains four steps for acquiring information from research articles to be used in the review. The first step is to define a set of focused research questions. Second, to establish key terms and search through the literature. Third, is to screen papers using inclusion criteria previously formed. Finally, the fourth step is to create a classification scheme for the papers. Since this systematic literature review focuses on the connection between $PM_{2.5}$ and Alzheimer's disease, the three defined research questions (RQs) to focus our search are the following:

RQ1: What are the biological mechanisms through which $PM_{2.5}$ exposure contributes to the onset or progression of Alzheimer's Disease?

RQ2: What are the public health implications of the relationship between $PM_{2.5}$ exposure and Alzheimer's Disease, and how can these inform policy decisions?

RQ3: What is the economic impact of $PM_{2.5}$ exposure related to Alzheimer's Disease on society?

The key terms used to search through the literature were $PM_{2.5}$ and Alzheimer. The two key terms were simultaneously searched using the AND operator. The searches were performed using these two keywords on two electronic databases that are reliable and known to cover peer reviewed articles and scientific journals. The two being the UCSB Library advanced search system and PubMed. Using the two keywords in a 'contains' search, 447 appeared articles to choose from. Due to the limited time given to write this review, fewer articles could be sifted through for relevant research than is typical for professional systematic literature reviews. This means that the search must be greatly narrowed down compared to professional systematic

literature reviews. To do this the search was altered, first changing the $PM_{2.5}$ to a title only search. This resulted in 126 articles to choose from. Next, the timespan limited to articles published after 2015. This resulted in 80 articles to choose from. Out of these articles only the first 5 pages of the website were used in the search containing 10 articles per page.
For these 50 articles, the primary search only addressed the titles, choosing ones that seemed to match the given RQs. After a brief sift through the 5 pages, a lack of research articles centered around the third RQ was found. Due to this one more key term, economic, was added with an AND operator. This resulted in 10 research articles specific to the third RQ. Finally, as the article was being written the need for greater accuracy in the first RQ arose. Searching through PubMed using the keyword “amyloid hypothesis”, with the quotations and no earlier than 2020, resulted in 169 results of which one was chosen based on abstract reading.

Database	Keywords	Location of Keyword (respectively)	Earliest Date	# of results	# of chosen
UCSB Library	PM2.5, Alzheimer's	Any, Any	Any	447	0
UCSB Library	PM2.5, Alzheimer's	Title, Any	Any	126	0
UCSB Library	PM2.5, Alzheimer's	Title, Any	2020	80	8
UCSB Library	PM2.5, Alzheimer's, Economic	Any, Any, Any	2020	10	3
PubMed	"Amyloid Hypothesis"	Any	2020	169	1

Results

Biological Mechanisms Linking $PM_{2.5}$ and Alzheimer’s Disease

Two key studies provide biological insights into the connection between $PM_{2.5}$ exposure and Alzheimer’s Disease. These studies examine the effects of $PM_{2.5}$ on biological tissue, identifying disrupted or altered biological tissue. Each study employs a different approach: the first uses mice to investigate the specific biological effects $PM_{2.5}$ has on the brain, while the second examines the brains of dogs, children, and teenagers to provide a more accurate representation of human responses.

The mouse model study [4], a three-month-long controlled experiment, was performed on two groups of mice. The control group contained mice exposed to clean, filtered air while the experimental group was continuously exposed to real-world $PM_{2.5}$ levels. Throughout the 3-month period and afterward, both groups of mice were extensively tested using reliable forms of assessment. Changes in cognitive and motor functions were assessed using the Morris Water Maze and rotarod tests. Magnetic resonance imaging was utilized to identify any significant changes in brain volume, while tissue samples were examined using hematoxylin and eosin staining, Nissl staining, and immunohistochemistry to observe microstructural alterations following $PM_{2.5}$ exposure. Finally, the levels of Alzheimer's disease related proteins were quantified using Western blot analysis. The findings of the study show no cognitive or motor function differences but an obvious neuronal loss, as well as increased levels of phosphorylated-tau and MDA in the olfactory bulb. However, surprisingly, no amyloid pathology was detected. In addition, the induced neurodegenerative changes in the brain follow the nasal entry and spread route typical to $PM_{2.5}$. This strongly suggests that most, if not all, of the changes observed were caused by $PM_{2.5}$.

Lilian Calderon-Garciduenas et al. [9] examined the effects of $PM_{2.5}$ on the brains of dogs, children, and teens in the Mexico City Metropolitan Area (MCMA). Subjects from the MCMA were compared to a control group gathered from areas that fulfilled two criteria: a population less than 75,000 and air pollutant levels lower than the 2015 US EPA standards. All of the subjects gathered were previously deceased with animals coming from former studies and human subjects obtained from forensic cases with no identifiable personal data. The study used light microscopy as well as Transmission Electron Microscopy (TEM) to examine the prefrontal white matter areas of the brain. Major findings included inflammation in the cerebrovascular basement membrane along with small deposits of amyloid-β in human subjects, a major indicator for Alzheimer's disease development.

These studies provide a foundational understanding of biological mechanisms linking $PM_{2.5}$ exposure to AD. By detailing the biological changes observed in animal models and human samples, they highlight potential impact of $PM_{2.5}$ on the progression of AD. Building upon this biological framework, the following research shifts to explore the epidemiological evidence and socio-economic consequences associated with $PM_{2.5}$ exposure, further defining the broader implications of this environmental risk factor on society.

Epidemiological Correlations Between $PM_{2.5}$ Exposure and Alzheimer's Disease

A Canadian study created a retrospective open cohort of older adults to assess the correlation between distance to road and AD hospitalizations [11]. An experimental group from Quebec and a control group from the island of Montreal were used. Data was gathered from the Quebec Integrated Chronic Disease Surveillance System for the period from January 1, 2000, to December 31, 2012. Each participant was assigned average annual concentrations of $PM_{2.5}$ as well as the distance to major roads. An algorithm used by the public health institutions of Quebec for Alzheimer's Disease was then applied to find the association between $PM_{2.5}$ and Alzheimer's disease in the participants. The results show a low but significant association

between the two variables with an average hazard ratio (HR) of 1.43. Taking into account the roads, those furthest away were found to have a 0.998 HR, while those closest had a 2.05 HR, with a confidence interval of 95%.

A study was conducted to find the relationship between $PM_{2.5}$ and the seasons [8]. In addition, the researchers also monitored neuronal cultures while conducting the study. Researchers collected $PM_{2.5}$ samples with middle volume air samplers in Taiyuan, China, for a period of one year, from March 2012 to March 2013. To assess the neuronal cultures, Kunming mouse pups were sacrificed by cervical dislocation and immediately incubated. Two groups were formed: an experimental group treated with different levels of $PM_{2.5}$ and a control group incubated in saline. The findings revealed significant differences between spring, summer, winter, and fall. The pro-apoptotic gene increased to 1.56, 1.11, 1.37, and 2.19 times the control, respectively. The protein level of the anti-apoptotic gene showed the opposite result, at 0.82, 0.90, 0.85, and 0.78 times the control, respectively.

The final studies shift the focus from understanding the mechanisms and correlations to assessing the practical implications of $PM_{2.5}$ exposure on society. They evaluate the economic burden and public health impact of $PM_{2.5}$-related AD, offering insights into how environmental factors translate into substantial societal costs.

Socio-Economic Impacts of $PM_{2.5}$-Related Alzheimer's Disease

A study on the monetary effects of $PM_{2.5}$, specifically regarding AD, was conducted in Sweden in an attempt to address the aging population problem [5]. Data on the average population-weighted exposure to ambient $PM_{2.5}$ was gathered, as well as the estimated annual number of AD cases attributed primarily to $PM_{2.5}$. The researchers estimated the monetary burden based on costs related to AD, including indirect and direct lifetime costs. The results found that an annual number of 820 AD cases can be attributed to $PM_{2.5}$, representing 5% of all cases in Sweden. The average lifetime cost of AD per case was estimated to be 213,000 euros. Researchers suggest that an attempt to improve the $PM_{2.5}$ concentrations, stating that a reduction of only a 1 microgram/m^3 would lead to a monetary benefit of 0.01% of the Swedish GDP.

A similar study performed in China assessed the short-term association between $PM_{2.5}$ and AD, as well as the economic costs [10]. A total of 4975 cases of AD patients hospitalized between 2017 and 2019 were collected. In addition, data on $PM_{2.5}$ were obtained from 182 air quality monitoring stations in the Sichuan Province. A time series-generalized additive model was used to estimate the association between the two variables, stratified by gender, age, and season. The results found that 16.48% of AD hospitalizations were attributed to the effect of $PM_{2.5}$. The total economic cost calculated by the researchers was 2.56 million US dollars.

Discussion

The overarching question addressed in this systematic review was: What are the correlations, mechanisms, and effects of the relationship between $PM_{2.5}$ and Alzheimer's Disease. Each research question helped narrow down the area of research around this topic. The first question

focused on how $PM_{2.5}$ is involved in the biological processes that occurs during the development of AD. One of the leading hypotheses on the indicators for AD is the Amyloid Cascade hypothesis [12], which shows that rising levels of amyloid-β are strong indicators for developing AD. In the Mexico City study [9], small deposits of amyloid-β were found in human subjects that had been exposed to high levels of $PM_{2.5}$. However, in the controlled mouse experiment [4], there was no amyloid pathology detected indicating that the levels of amyloid-β between the control an experiment groups did not change. This result could be due to the short-term nature of the study, however, as other indicators such as increased levels of phosphorylated-tau and inflammation of the olfactory bulb are also signs of developing AD albeit not as strong of a connection as amyloid-β. All these studies show the possibility that $PM_{2.5}$ can directly contribute to developing AD as well as the mechanisms behind it.

The second research question focuses on examining the correlation between $PM_{2.5}$ and AD as well as how different factors affect the relationship. For example, the Canadian study addressed the HR of $PM_{2.5}$ on AD considering the distance to roads. Vehicles are a leading producer of $PM_{2.5}$ meaning the proximity of roads also serves as an estimate of the level of $PM_{2.5}$ exposure. The study showed more than a full point HR between those furthest and those closest being 0.998 and 2.05 respectively. HR is used to estimate the danger of a certain factor based on the average. A 1.0 HR means that you have an average level of danger while 2.0 means twice as dangerous as the average. Having an HR of 2.05 due to only distance from roads is concerning for community health. A factor of seasons was introduced by [8] showing the large differences in pro-apoptotic gene expression throughout the year. Pro-apoptotic genes are a natural biological mechanism whose function is to administer programmed cell deaths. However, if an unnatural amount of Pro-apoptotic genes are produced the amount of cell death can cause damage to the system. Amyloid-β is a protein that, when accumulated, induces apoptosis of the brain's cells [3]. Amyloid-β's link to $PM_{2.5}$ can be seen in the seasons. Earth's seasons have been shown to directly correlate with $PM_{2.5}$ concentration having winter at the highest levels. As [8] shows, winter also has the highest pro-apoptotic gene expression of 2.19 times the control with clean air. While this is not conclusive due to the nature of correlations it still suggests some credibility of AD development towards $PM_{2.5}$.

The final research question serves to put the topic of the review into a more tangible perspective. The economic consequence is difficult to assess but easy to review. The two articles in the review already performed the challenging part of assessing the monetary value. Their findings show that $PM_{2.5}$ represents a marginal portion of AD cases being estimated at 5% for Sweden [5] and 16.48% for Sichuan, China [10]. If we estimate the world's percentage to be the average of the two, we get 10.74% of all AD cases attributed primarily to $PM_{2.5}$. The Sweden study estimated the average lifetime cost of one case of AD to be 213,000 euros. With 4.2 million people being diagnosed with AD every year, and 451,080 being attributed to $PM_{2.5}$ the total societal cost is estimated at 96 billion euros. That is a staggering amount for such a little particle of pollution.

Various limits to the study must be addressed, for starters, the lack of time to sufficiently research the topic of the review. Certain areas such as the biological mechanisms are incredibly

complex, requiring experts to properly connect what is occurring in the body. Another limit to the review is the lack of data specifically on the link between AD and $PM_{2.5}$. Many of the studies gathered were primarily about dementia and neurodegenerative disease as a whole in regard to $PM_{2.5}$. Future research should focus more on the exact disease wanting to be assessed and not group diseases such as AD and Parkinson's together. Also, future longitudinal experiments are required to precisely judge $PM_{2.5}$'s effect on AD. Studies, such as the mouse experiment, are only conducted for short terms. Whereas the necessary data should be gathered over years of research. The current studies that have used former years of data can only be correlational, due to the lack of experiments, which leads to a lack of causal findings. Future literature should focus on monitoring the brain's reaction to $PM_{2.5}$ for long periods, focusing on the indicators of AD and how they change.

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