



## “ASSOCIATION BETWEEN PARTICULATE MATTER AND ALZHEIMER'S DISEASE IN ELDERLY SUBJECTS”

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### Introduction:

Alzheimer's disease (AD) is an age-related, progressive, neurodegenerative disorder, affecting more than 4 million people in the US and more than 30 million people worldwide [1]. The pathological changes seen in the brain are plaque formations consisting mainly of amyloid beta ( $A\beta$ ) protein deposits surrounded by neurons containing neurofibrillary tangles. Associated with  $A\beta$ -containing senile plaques are reactive microglia and activated macrophages producing cytokines like IL-1, IL-6 and TNF- $\alpha$ , as well as acute phase proteins, indicating inflammation [2]. Also associated with the plaque deposition is vascular damage and neuronal loss in the area of hippocampus and frontal cortex, leading to severe memory loss [3, 4].

Environmental gases like ozone, together with particulate matter (PM) and organic compounds, in outdoor and indoor air forms the complex mixture of air pollution [4]. Studies indicate that chronic exposure to particulate matter may increase oxidative stress by producing reactive oxygen species (ROS) and chronic neuroinflammation, which may be forerunners for AD and other neurodegenerative disorders [1, 3, 5]. Findings indicate that there is an association between particulate matter and neurodegenerative processes [2, 5]. Animal studies have added to the concerns that air pollution containing PM may contribute to AD and other CNS outcomes through some of the mechanisms presented above ([3] Increasing size of the aging population may in part explain the increasing incidence of AD, but environmental factors like particulate matter may also be an important contributing factor [3].

Increasing AD incidence with accompanying cognitive decline and memory loss poses serious economic, social and health delivery problems at a global scale. Studies have indicated that air pollution, largely caused by increasing urbanization [2, 6] and [7] may be of etiologic importance. After going through various studies showing a possible relationship between PM and AD I wanted to test the hypothesis that an association exists between exposure to PM and AD. Air pollution containing PM, ozone, carbon monoxide, nitrogen dioxide, sulfur dioxide, and lead is largely found in urban atmosphere. In this review paper my focus is on ambient air PM. Several studies have demonstrated the ability of PM to cross the blood-brain barrier and reach the CNS. However, PM may also reach the brain through the systemic circulation. Hence the purpose of this review paper is to explore the relationship between ambient air PM and AD in elderly subjects in order to learn whether AD may be, to some extent, a preventable disease.

### Methods:

Studies were identified by searching PubMed, Google Scholar, and Scopus, keeping Air pollution, Particulate Matter, Alzheimer's disease, Cognitive Impairments and Dementia as the main searching words. In this systematic review we wanted to include all published studies that provide results of AD among patients exposed to ambient air PM in the general population. For inclusion into the systematic review papers, therefore, the following criteria had to be met: study subjects had to be recruited at the population level (i.e., not hospital based) to make them representative of the underlying population and less susceptible to selection bias. Different

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designs were included to look at different aspects of ambient air PM in relation to AD risk: Studies with case control designs because they in a short time frame gives indications of causality, and longitudinal designs and because they show the results of long term exposure of particulate matter on cognitive function with correct time sequence of exposure and outcome. Cross sectional studies were included to determine the association between PM exposure and cognitive functions in older US adults presently available. To explore the biological plausibility of PM as a risk factor for AD experimental studies on animals and histopathological studies on young

children and young adults were included to determine the route of entry of PM and the associated changes in the brain typical of AD. Studies having searching words as “cognitive impairments” and “dementia” were included, as were studies of the prevalence of AD in patients with established dementia. The titles and abstracts of all articles identified by the search were screened and potentially relevant articles were retrieved and assessed according to the criteria mentioned above. Meticulous search for articles on the topic of Association between PM and AD started in June 2014.

**Results:**

**TABLE 1. Results of the PubMed search.**

STUDY	OBJECTIVE	SUBJECT	VARIABLES	RESULTS
(Gatto, Henderson 2014) [8] Cross Sectional Study.	To explore the effect of air pollution on Cognitive function.	1,496 healthy cognitively Intact adults.	PM <sub>2.5</sub> , O <sub>3</sub> , NO <sub>2</sub> , Age, gender, race, education, income, study, mood	None of the pollutants (PM <sub>2.5</sub> , O <sub>3</sub> , NO <sub>2</sub> ) were significantly associated with global cognition. Increasing exposure to PM <sub>2.5</sub> was related to lower verbal learning β = -0.32 (95% CI: -0.63,0.00) per 10 µg/m <sup>3</sup> PM <sub>2.5</sub> , p = 0.05
(Weuve,Puett 2012) [9] Nurses' Health Study Cohort	To explore the relation of cognitive decline on long term exposure to PM both coarse (PM 10µm, 2.5µm) and fine (<2.5µm).	19,409 Nurses aged 70-81 years. Measurement period: 7-14 years	PM (coarse and fine), cognitive function.	Difference in 2 year change (95% CI) in global cognitive score: <b>A. Per 10µg/m<sup>3</sup> increment in exposure:</b> <ul style="list-style-type: none"> <li>PM<sub>2.5-10</sub>: -0.020 (-0.032 to -0.008)</li> <li>PM<sub>2.5</sub>: -0.018 (-0.035 to -0.02)</li> </ul> <b>B. In highest vs lowest quintile of exposure:</b> <ul style="list-style-type: none"> <li>PM<sub>2.5-10</sub>: -0.024 (-0.040 to -0.008)</li> <li>PM<sub>2.5</sub>: -0.018 (-0.034 to -0.002)</li> </ul>

**TABLE 1 (cont). Results of the PubMed search.**

STUDY	OBJECTIVE	SUBJECT	VARIABLES	RESULTS
(Ranft 2009) [6] Cohort Study.	To assess the relation of PM <sub>2.5</sub> to mild cognitive impairment that are associated with high risk of AD .	399 women 68 to 79 years of age with > 20 years of PM exposure	Air pollution, Lung function, Inflammation, Aging.	CERAD-Plus points (95% CI): A. according to traffic exposure: <ul style="list-style-type: none"> <li>Age ≤ 74: -3.8 (-7.9, 0.4)</li> <li>Age &gt; 74: 0.3 (-7.3, 7.8)</li> </ul> B. According to distance to next busy street: <ul style="list-style-type: none"> <li>-1.6 (-3.2, 00) (p≤0.05)</li> </ul>
(Ailshire & Clarke, 2015) [10] Cross- Sectional Study.	To determine the association of PM <sub>2.5</sub> in residential environment to cognitive function.	780 non-Hispanic black, white men and women age 55+	Cognition, Age, Education, PM, gender, Neighborhood.	Regression of Count of Errors-PM <sub>2.5</sub> , 10 µg/m <sup>3</sup> increment: OR=1.53 (95% CI: 1.02-2.30) Those living in areas with greater exposure to PM <sub>2.5</sub> had an error rate 1.5 times greater than those exposed to lower PM <sub>2.5</sub> concentration

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(Calderon-Garciduenas 2004) [2] Human Autopsy Study	To determine the association of air pollution and brain inflammation in resident of high air pollution.	Brain samples: A. 10 from highly polluted areas (Mexico city and Monterrey) B. 9 from small cities with low level of pollution	Air pollution, inflammation, neurodegeneration, AD.	A strong positive correlation was found between: <ul style="list-style-type: none"> <li>• COX2 mRNA levels and</li> <li>• Oxidative DNA damage by AP* sites</li> </ul> (r = 0.89, p = 0.001, Spearman and Pearson) in frontal cortex of high-exposure group, but not in subjects of low air pollution areas. <p>*apurinic &amp; apyrimidinic sites (inhibits DNA replication, increases base substitution mutations and loss of genetic integrity)</p>
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TABLE 1 (cont). Results of the PubMed search.

STUDY	OBJECTIVE	SUBJECT	VARIABLES	RESULTS
(Calderon-Garciduenas 2003) [11] experimental Study	To determine the effect of PM on nervous system.	Dogs n=26 from Mexico City [MC] or low levels of air pollution (n=14 from Tlaxcala [TC])	PM, AD, Urban Population, Olfactory Pathology, BBB, DNA oxidative damage.	Mean AP* sites/10 <sup>6</sup> nucleotides in: <ul style="list-style-type: none"> <li>• MC dogs: 12.5 ± 1.7</li> <li>• TL dogs: 3.9 ± 0.8</li> <li>• (p=0.0002).</li> </ul> MC dogs had AD like brain changes: <ul style="list-style-type: none"> <li>• Atrophy of cortex</li> <li>• β-amyloid plaques</li> <li>• Neurofibrillary tangles</li> </ul> *apurinic & apyrimidinic sites (inhibit DNA replication, increases base substitution mutations and loss of genetic integrity)
(Jung, Hwang 2014) [12] Cohort Study	To determine the long term association between particulate matter and ozone with newly diagnosed Alzheimer's disease in Taiwan.	95,690, individuals aged above 65 during 2001-2010	PM, AD, Neurodegeneration.	The data were analyzed in a Cox Regression model. The risk of AD was found to increase 138% per 4.34 µg/m <sup>3</sup> increase in PM <sub>2.5</sub> over the follow up period (95% CI 2.21-2.56). Findings suggest that long term exposure to PM <sub>2.5</sub> is associated with increased risk of Alzheimer's disease
(Campbell 2005) [4] Experimental study	The purpose of this study is to find out the effects of PM <sub>2.5</sub> and PM <sub>0.18</sub> on the brain of mouse.	Mice. (Male BALB/c 6 weeks old) exposed to concentrated ambient PM in a heavily polluted urban environment for 2 weeks vs controls	PM, Inflammation, Neurodegenerative disease.	Level of proinflammatory cytokines in the cytoplasmic fraction of the brain after exposure to: <p>PM<sub>0.18</sub> (mean 285.5µg/m<sup>3</sup>): TNF-α increased ≈ 15% (ns)</p> <p>IL-1α increased ≈ 2.8x (p&lt;0.05)</p> <p>[PM<sub>0.18</sub>+PM<sub>2.5</sub>](mean 441.7µg/m<sup>3</sup>):</p> <p>TNF-α increased ≈ 50% (p&lt;0.05)</p> <p>IL-1α increased ≈ 3.4x (p&lt;0.05)</p>

TABLE 1 (cont). Results of the PubMed search.

STUDY	OBJECTIVE	SUBJECT	VARIABLES	RESULTS
(Calderon-Garciduenas 2008) [13] Case Cohort Study	This study was done to determine the role of PM <sub>10</sub> and PM <sub>2.5</sub> on neurodegenerative changes as seen in highly polluted places like Mexico City	47 Children and young adults of 2-45 years of age who die suddenly.	PM <sub>10</sub> and PM <sub>2.5</sub> , AD, α-synuclein, Amyloid β42	In highly polluted areas (MC) vs less polluted areas (control cities) significant higher levels found of: <ul style="list-style-type: none"> <li>• Frontal cortex: <ul style="list-style-type: none"> <li>- COX2 mRNA (p=.008)</li> <li>- IL-1β mRNA (p=.0002)</li> </ul> </li> <li>• Olfactory bulb (OB): <ul style="list-style-type: none"> <li>- COX2 mRNA (p=.0002)</li> <li>- IL-1β mRNA (p=.003)</li> <li>- CD14 rRNA (p=.04)</li> </ul> </li> </ul>

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	in children and young adults who suddenly die of neurological problems	N=35 from highly polluted area. N=12 from less polluted area.		
(Anna Oudin, 2016) Cohort Study. [14]	This cohort study was designed to find out the relationship between long term exposure of traffic pollution and dementia.	1806 participants from a major city in Sweden	Ambient air pollution, dementia, AD	Participants in the group with the highest exposure were more likely than those in the group with the lowest exposure to be diagnosed with dementia (Alzheimer's disease or vascular dementia), with a hazard ratio (HR) of 1.43 (95% CI: 0.998, 2.05 for the highest vs. the lowest quartile). The estimates were similar for Alzheimer's disease (HR 1.38) and vascular dementia (HR 1.47). The HR for dementia associated with the third quartile versus the lowest quartile was 1.48 (95% CI: 1.03, 2.11).
(Hong Chen 2017) Population based Cohort study. [15]	To determine the relationship between air pollution and dementia in a place like Ontario Canada where the air pollution is lowest.	2066'639 adults with mean age 66.8 years	PM <sub>2.5</sub> , NO <sub>2</sub> , and O <sub>3</sub> , dementia	<p><b>Exposure</b></p> <p>PM<sub>2.5</sub> 2.4% (1.8-3.0%)  NO<sub>2</sub> 5.4% (4.4-6.6%)  PM<sub>2.5</sub> + NO<sub>2</sub> 6.1% (4.8-7.5%)</p> <p><b>Dementia</b></p> <p>PM<sub>2.5</sub> 6278 (4738-7816)  NO<sub>2</sub> 13,962 (11,428-16,910)  PM<sub>2.5</sub> + NO<sub>2</sub> 15,813 (12,374-19,464)</p>
(MCacciottolo Cohort study. [16])	To determine the harmful effects of air pollutant to brain of older women in US and in AD transgenic mice.	173 as incident case of all cause dementia with average 9.9 years follow up.	PM <sub>2.5</sub> , dementia, AD	During the follow up of 9.9 years 392 subjects had global cognitive decline. Female EFAD mice were chronically exposed to nPM during 15 weeks. Increased amyloid deposition was observed as fibrillary amyloid by ThioS binding and by 4G8 plaque immunohistochemistry that were greater for E4FAD mice than E3FAD. For ThioS nPM exposure increased amyloid load by + 60% in E4FAD above non exposed controls (P 0.048) whereas E3FAD did not respond (P 0.79)

Gatto NM et al. [8] assessed cognitive function in 1,496 subjects (females: 79.4% mean age  $\pm$  SD: 60.5  $\pm$  8.1 year), with a battery of neuropsychological tests. Effects were estimated using regression models of air pollutants on cognitive function adjusting for age, gender, race, education, income, study and mood. None of the pollutants (PM<sub>2.5</sub>, O<sub>3</sub>, NO<sub>2</sub>) were significantly associated with global cognition. Increasing exposure to PM<sub>2.5</sub> was associated with lower verbal learning ( $\beta$  = -0.32 per 10  $\mu\text{g}/\text{m}^3$  PM<sub>2.5</sub> 95% CI = -0.63, 0.00; p = 0.05). Ambient exposure to > 20ppm versus  $\leq$  10 ppm of NO<sub>2</sub> was associated with lower logical memory ( $\beta$  = -0.62, 95% CI + -1.35, 0.03; p = 0.059). Ambient O<sub>3</sub> exposure ( $\leq$  34ppm versus > 49 ppm) was associated with lower executive function ( $\beta$  - 0.66, 95% CI = -1.35, 0.03; p = 0.059). Men had higher exposure of PM<sub>2.5</sub> (20.2  $\pm$  3.5 versus 16.5  $\pm$  3.3  $\mu\text{g}/\text{m}^3$ , p < 0.0001) than women. Men also had higher exposure to NO<sub>2</sub> than women (29.1  $\pm$  7.1 versus 24.3  $\pm$  6.3 p < 0.0001). Caucasian population had less exposure to PM<sub>2.5</sub> than Latin, African American or Asian

participants (p values < 0.05). Participants with lower educational levels or household incomes had greater exposure to PM<sub>2.5</sub>. This cross-sectional study concluded that there was an association between higher exposure to PM<sub>2.5</sub>, O<sub>3</sub>, and NO<sub>2</sub> and lower cognitive abilities among healthy cognitively intact adults.

Weuve J et al [9] report from Nurses Health Study Cognitive Cohort of 19,409 women aged 70 to 81 years. In this study short term (one month) exposures to PM<sub>2.5-10</sub> and PM<sub>2.5</sub>, and long term (7-14 years follow-up, 2 year change) exposures to PM<sub>2.5-10</sub> and PM<sub>2.5</sub> were analyzed. A significantly faster cognitive decline was observed with higher levels of long term exposure to both PM<sub>2.5-10</sub> and PM<sub>2.5</sub>. The multivariate adjusted analysis found rates of change in global cognitive function score standard units that was worse with higher levels of long term exposure to both PM<sub>2.5-10</sub> (p trend= 0.01) and highest versus lowest quintile of exposure (p=0.003). The higher estimated PM<sub>2.5-10</sub> exposures during the periods of one year, two

years, and five years were also associated with significantly worse decline in the global cognitive score. For PM<sub>2.5</sub> women in the highest quintile of long term exposure had significantly worse rates of change in global score than did women in the lowest quintile (p = 0.03). The trends across quintiles of exposure (p= trend 0.11). However modeling PM<sub>2.5</sub> as a continuous variable both five years exposure and more than five years exposure were associated significantly worse global cognitive decline. Long term exposure to PM<sub>2.5</sub> was found to be a much better predictor of decline in the individual cognitive ability as compared to recent PM<sub>2.5</sub>. The two years results for pM<sub>2.5-10</sub> and PM<sub>2.5</sub> in rates of global cognitive change per 10µg/cm<sup>3</sup> given are (-0.20[95% CI -0.032 to -0.008] and -0.018[-0.035 to -0.002] respectively. Therefore the nurses health study concluded that long term exposure to higher levels of both PM<sub>2.5-10</sub> and PM<sub>2.5</sub> was associated with worse cognitive decline yet the results are worse for exposure to PM<sub>2.5</sub>.

Ranft U et al [6] investigated the association between PM<sub>2.5</sub> and mild cognitive impairment (MCI) which carries a high risk progression to AD. This cohort study included a sample of 399 women aged 68-79 years who had been living for more than 20 years at the same residential address. The relation between traffic related fine PM and MCI were studied. The distance of study subjects' residence from the busy roads were assessed to get an idea of chronic exposure to traffic related PM that be involved in the pathogenesis of Alzheimer's disease. The regression analysis showed that for women aged 74 years or less, distance from busy traffic roads was a significant and consistent factor for MCI. If the distance from a busy road with traffic density of more than 10,000 cars was more than 50m then there test were significantly reduced indicating decline in MCI. It is very surprising that no adverse effects of traffic exposure on MCI was seen in women older than 74 years. Traffic exposure in women ≤ 74 years was on the average reduced by 3.8 points ( 95% CI 7.9,0.4) while in women aged ≥ 74 years it was increased by 3 points ( 95% CI -7.3, 7.8). In this study the long term exposure to elevated broad scale PM<sub>10</sub> back ground concentration could not be distinguished but the effect for urban and rural environments were detected very well. According to distance to next busy street, -1.6 (-3.2, 00) (p≤0.05). The sample size for women older than 74 years was very small that is only seven women were taken. This small size of women older than 74 years could be the reason for not detecting the positive results for exposure

to traffic related PM. There could be other reasons such as, these women might be living away from high traffic area, or due to increasing age restricted mobility and lack of interest women are unlikely to participate in health related programs. In addition to this there could be other reason such as with increasing age there is an increased risk of MCI that may mask the traffic related effects when test for MCI are performed.

The objective of the study by Ailshire & Clarke [10] was to explore the relation between exposure to fine particulate matter (PM<sub>2.5</sub>) and cognitive ability in the Americans Changing Lives (ACL) survey of older US adults. In this cross sectional study, 780 non-Hispanic black and white men and women aged 55 years and older from the 2001/ 2002 survey was assessed. Negative binomial regression models were used to examine the association between PM<sub>2.5</sub> and the cognitive functions. Average PM<sub>2.5</sub> exposure was 13.8 µ/m<sup>3</sup> while the national ambient air quality standard that is determined by the EPA to be the level at which there is an increased risk to human health is 12 µg/m<sup>3</sup>. About two thirds of the respondents were found to be living in areas where the PM<sub>2.5</sub> concentration in the atmospheric air exceeded the air quality standard. According to model 1 (unadjusted association between PM<sub>2.5</sub> and the cognitive errors). People living in areas of high PM<sub>2.5</sub> air pollution had an error rate of 1.7 (IRR = 1.69 [95% CI, 1.10-2.59]) times greater than those living in low pollution surroundings. In Model 2 after accounting for key individuals and neighborhood level characteristics like age, gender, race education, marital status and income the association between PM<sub>2.5</sub> and cognitive errors are reduced but remains statistically significant (p < 0.05). People living in areas with exposure to higher air pollution having dense concentration of PM<sub>2.5</sub> had about 50% higher error rate compared to greater impairment of cognitive ability than those exposed to low concentration of PM<sub>2.5</sub>.

Regression of Count of Errors- PM<sub>2.5</sub>, 10 µg/m<sup>3</sup> increment: OR=1.53 (95% CI: 1.02-2.30). Those living in areas with greater exposure to PM<sub>2.5</sub> had an error rate 1.5 times greater than those exposed to lower PM<sub>2.5</sub> concentration. The results of this study suggest that habitual high exposure to PM<sub>2.5</sub> in air may have an adverse effects on cognitive function of older adults.

Calderon-Garciduenas L et al. [2] investigated the inflammatory response associated with air pollution and neuro degeneration in brain tissue of elderly subjects.

The expression of cyclooxygenase-2 (COX2), an inflammatory mediator and accumulation of 42-amino acid form of  $\beta$ -amyloid (A $\beta$ 42), a cause of neuronal dysfunction, were measured in autopsy brain tissue in cognitively and neurologically intact lifelong residents of cities with low air pollution and high air pollution. A total of 19 study subjects of which 9 subjects were severely exposed to air pollution and 10 subjects were exposed to low air pollution. The brain tissue of these subjects was examined, and the frontal cortex showed an elevation of COX2mRNA levels in the high exposure group ( $p = 0.009$ , Mann-Whitney test). There was an elevation of COX2 immuno-reactivity in subjects of high exposure group which was confirmed by quantitative image analysis of COX2 immuno-reactivity (IR) ( $p = 0.01$ , Mann-Whitney test). In subjects that were from the areas of low air pollution the COX2 IR was confined to neuronal cell bodies, whereas subjects from high air pollution group exhibited COX2 staining of endothelium both in cortex and white matter blood vessels. In 15 subjects for which hippocampus tissue was available COX 2 mRNA was also elevated in subjects who were from high air pollution cities ( $p = 0.045$ , Mann-Whitney test). The average COX2 IR density was greater in the high air pollution group, but it was not significantly different from levels in low air pollution group subjects ( $p = 0.37$ ). A strong positive correlation was found between COX2 and mRNA levels and oxidative DNA damage by AP sites ( $r = 0.89$ ,  $p = 0.001$ , Spearman and Pearson) in frontal cortex of high-exposure group, but not in subjects of low air pollution areas. There was no correlation of COX2 mRNA levels and AP sites in hippocampus. However in addition to up regulation of COX2 expression A $\beta$ 42 IR was increased in the frontal cortex ( $p=0.04$ ) and in hippocampus ( $p=0.001$ ) in the high exposure group. The authors concluded that exposure to urban air pollution may cause brain inflammation and accelerates the accumulation of A $\beta$ 42, a putative mediator of neurodegeneration and AD pathogenesis.

Calderon-Garciduenas et al. [11] in this study explored the role of ambient PM on brain tissue and other organs such as the cardiovascular system and the respiratory system. This study was done on dogs exposed to high levels of air pollution ( $n=26$  from Mexico City [MC]) or low levels of air pollution ( $n=14$  from Tlaxcala [TC]). On Necropsies nasal mucosa, olfactory bulb, and brain tissues were examined for PM<sub>10</sub> and PM<sub>2.5</sub>. Air pollutants measured included PM<sub>10</sub> and PM<sub>2.5</sub>. Apurinic and apyrimidinic (AP) sites inhibit DNA replication,

promotes base substitution mutations and causes loss of genetic integrity. Mean AP sites were significantly higher in MC dogs compared with controls in OB (controls  $3.9 \pm 0.8$  vs MC  $12.5 \pm 1.7$  ( $p= 0.0002$ ). In the brain tissue of MC dogs Alzheimer like changes including atrophy of cortex,  $\beta$ -amyloid plaques and neurofibrillary tangles were seen.

Jung CR et al. [12] investigated the association between long term exposure to ambient PM and ozone with newly diagnosed AD in Taiwan. This was a cohort study of 95,690 individuals aged 65+ during 2001- 2010. Between 2001 and 2006 PM<sub>10</sub> was studied and from 2006 - 2010 PM<sub>2.5</sub> since PM<sub>2.5</sub> data was only accessible after 2006. Mean of both PM<sub>10</sub> and PM<sub>2.5</sub> was used to estimate the PM<sub>2.5</sub> concentration from 2001-2005. The data were analyzed in a Cox Regression model. The risk of AD was found to increase 138% per  $4.34\mu\text{g}/\text{m}^3$  increase in PM<sub>2.5</sub> over the follow up period (95% CI 2.21-2.56). These findings suggest that long term exposure to PM<sub>2.5</sub> is associated with increased risk of Alzheimer's disease.

Campbell A, et al [4] did an experimental study to investigate the effects of exposure (4 hours, 5 days/week for 2 weeks) to PM<sub>2.5</sub> and PM<sub>0.18</sub> on the brain of ovalbumin sensitized BALB/c mice. The difference among groups was assessed using one way analysis of variance followed by Tukey test. Results were considered statistically significant at  $p$  value less than 0.05 using a two tail distribution. Level of pro-inflammatory cytokines in the cytoplasmic fraction of the brain after exposure to: PM<sub>0.18</sub> (mean  $285.5\mu\text{g}/\text{m}^3$ ): TNF- $\alpha$  increased  $\approx 15\%$  (ns) IL-1 $\alpha$  increased  $\approx 2.8x$  ( $p<0.05$ ) (PM<sub>0.18</sub>+PM<sub>2.5</sub>, mean  $441.7\mu\text{g}/\text{m}^3$ ): TNF- $\alpha$  increased  $\approx 50\%$  ( $p<0.05$ ) IL-1 $\alpha$  increased  $\approx 3.4x$  ( $p<0.05$ ). The analysis of data of this study indicates that the inhaled PM may trigger a pro-inflammatory response in the nervous system that may lead to neurodegenerative changes in the brain. Pro-inflammatory cytokines TNF- $\alpha$ , and IL-1 $\alpha$  levels were determined in the cytoplasm of mice brains, the levels of IL-1 $\alpha$  were increased after fine or ultrafine particle exposure compared with filtered air exposure. TNF- $\alpha$  was increased after combined fine and ultrafine particles. ( $p= <0.05$ ) in controls.

Calderon-Garciduenas L et al. [13] did a case cohort study to determine the role of PM<sub>10</sub> and PM<sub>2.5</sub> on neurodegenerative changes as seen in highly polluted places like Mexico City in children and young adults who died suddenly. A sample ( $n=12$ ) was taken from low polluted

places like Tlaxcala and Veracruz and compared to a sample (n=35) from a highly polluted area. Average age was  $25.1 \pm 1.5$  with a range from ages of 2 to 45. After stratification of the data according to subject's residency, PCR analysis of COX2, IL-1 $\beta$  and CD14 mRNA was done. Rapid cycle PCR analysis of COX2, IL-1 $\beta$ , and CD14 in lungs, OB, frontal cortex hippocampus, substantia nigrae, periaqueductal gray and vagus nerves from 47 subjects indicated that the corresponding mRNA was present in each of the samples analyzed. For MC versus low polluted cities there was significant difference in COX2 mRNA in lungs (p=0.01), OB (0.0002), and frontal cortex (p=0.008). Significantly higher levels was found in brain tissue from MC of IL-1 $\beta$  mRNA in the frontal cortex (p=0.0002) and OB (p= 0.003) compared to controls. The higher IL-1 $\beta$  mRNA values for both OB and frontal cortex were seen in teens and young adults. CD14 values for OB was (p=0.04). This study indicates that ambient air PM may cause neuro-inflammation, an altered brain innate immune response, an accumulation of A $\beta$ 42 and  $\alpha$ -synuclein in the CNS, and that this process that may start in childhood could have the potential to cause AD like changes, and possibly be responsible for the development of AD later in life.

A Oudin in 2016 explored the occurrence of AD in both high air pollution area and lower air pollution places. [14] Average subjects were 1,086 and among these 191 were diagnosed with AD and 111 were diagnosed with vascular dementia. Patients in highest exposure were more likely to develop AD, or vascular dementia than patients in lowest exposure. (HR) of 1.43 (95% CI: 0.998, 2.05 for the highest vs. the lowest quartile). [14]The approximations were alike for Alzheimer's disease (HR 1.38) and vascular dementia (HR 1.47). The HR for dementia related with the third quartile vs the lowest quartile was 1.48 (95% CI: 1.03, 2.11).

H Chen tried to find out the relationship between dementia and air pollution at a place where the air pollution is lowest in the world and for this he choose Ontario City, where he found that even at lowest air pollution place the incidences of dementia were higher. [15]

M Cacciottolo in 2017 investigated the effects of air pollution in the brain of older women and mice. In his cohort study of 9.9 years he found harmful effects of urban air pollutants in the brain of elderly women in US and AD transgenic mice accelerate the formation of amyloid and degeneration of neurons.[16]

## Discussion:

The referenced studies (table 1) demonstrated a positive relationship between ambient air PM and neurodegenerative changes. Among these studies, five have epidemiological designs, of which three are cohort studies and two have cross-sectional designs. Four studies have reported histopathological changes in the brain according to exposure to ambient air PM, and indicating the route of entry of PM and demonstrating pathological changes associated with the exposure in dogs, in mice, and in humans, including children, young adults and elderly subjects.

The two cross sectional studies in table 1, by Gatto NM et al [8] and by Ailshire JA et al [10], demonstrated an association between ambient air PM<sub>2.5</sub> and cognitive impairment. Gatto NM et al. had a sample size of 1,496, and they probably had too little power to demonstrate a significant association between the pollutants (PM<sub>2.5</sub>, O<sub>3</sub>, and NO<sub>2</sub>) and global cognition. However, they did demonstrate a significant negative association between increasing exposure to PM<sub>2.5</sub> and verbal learning. Their findings were supported by Ailshire JA et al. in a racial diverse population of blacks and whites of both genders.

The findings by the Nurses' Health Study that long term exposure to increasing levels of PM<sub>2.5</sub> and PM<sub>2.5-10</sub>, is associated with increasing global cognitive decline in women [9] is important because it adds a dose response effect of ambient air PM<sub>2.5</sub> and PM<sub>10</sub> on cognition. This adds support to a possible causal relationship between ambient air PM and AD. The findings may indicate that the size of the exposure as well as the size of the particles may be related to the size of the neurodegeneration and pathological changes in the brain typical of AD [2,9,12]. These neurological changes may be of a progressive nature, initially causing only mild cognitive impairment. However, when the pathological changes in the brain has become extensive, symptoms of AD may become apparent [3,5]. These findings may indicate that the neurodegenerative processes associated with ambient air PM may have at least some features in common with the degenerative changes seen in the nervous system of elderly subjects with AD [1]

The findings by Ranft U et al that long term (>20 years) effects of traffic related PM<sub>2.5</sub> on decline in cognitive function was dependent on how close the traffic was to the residence of the subjects, indicate that ambient air PM<sub>2.5</sub> may have detrimental effect on the central nervous system

(CNS) [6]. These results are supported by earlier findings that ambient air  $PM_{2.5}$  and  $PM_{0.1}$  have been identified in human olfactory bulb, periglomerular neurons, and particles smaller than 100 nm have been found in intraluminal erythrocytes from frontal lobe and trigeminal ganglia capillaries, indicating a possible nasal olfactory pathway for the fine and ultrafine particles to enter CNS [3,5,14]. Experimental studies using animal models supports these findings. Calderon-Garciduenas L. et al, demonstrated on dogs the presence of  $PM_{2.5}$  and  $PM_{10}$  in the Olfactory bulb and brain tissue, supporting earlier toxicological studies reporting that one of the main routes of entry of PM to the CNS is through nasal passage [11, 14]. Findings thus indicate that ambient air PM may either enter through the nostrils, pass the blood brain barrier to reach the brain, or it may access the brain through the systemic circulation [5].

The exposure levels and particle size of ambient air PM, may be related to the speed of onset and to the gravity of the histopathological CNS changes, and to the neuro degeneration seen of a type similar with that of AD [2,12]. These changes in the brain seems to progress slowly at first, associated with only mild cognitive impairment, but when the pathological changes in the brain affects the neural tissues extensively the symptoms of AD may become more pronounced [1]. This scenario may explain findings from the autopsy studies where subjects in areas with high ambient air PM levels had higher levels of neuro inflammation, indicating a possible direct relationship between PM and degenerative changes in the central nervous system of elderly subjects [1, 2, 5].

Human autopsy studies on children, young adults and elderly subjects by Calderon-Garciduenas L, et al found increased inflammatory response in the brain of individuals who lived in areas with high ambient air pollution [2,13]. These findings are supported by animal studies. Campbell A, et al. found a pro-inflammatory response in the brain of mice exposed to fine and ultra-fine particles, and similar observations was done by Block, Peters and Veronesi [3, 14]. Further support is given by reports that air pollutants can act as pro-oxidants of both proteins and lipids, and promote oxidative stress and inflammatory responses by generating free radicals [1, 4, and 11]. More recent autopsy studies in humans have further indicated that ambient air pollution produces differential regulation of genes in the frontal cortex. These genes are "involved in multiple

functions like oxidative stress, inflammation, cell proliferation, differentiation and apoptotic death, DNA damage, presynaptic signaling, membrane trafficking, and microtubule assembly and stability" [1]. It has been proposed that air pollutants could be a risk factor for AD by representing a prevalent source of environmentally induced ROS production [1].

In the brains of dogs exposed to high levels of air pollution was found histopathological changes similar to changes seen in AD patients, with atrophy of cortex, formation of amyloid plaques, and neurofibrillary tangles [11]. The human and dog autopsy studies ( table 1), found significantly more AD like changes in the brain of subjects exposed to high ambient air pollution as compared to subjects living in low air pollution areas. This difference in the brain pathology according to exposure to ambient air pollution is indicative of a relation between cognitive ability and air pollution, particularly ambient air PM largely present in traffic related pollution [2,11,13]. These findings are supported by the recent report by Jung CR et. al. in a large cohort study with 95,690 individuals followed for 9 years where the risk of AD increased 138% per  $4.34 \mu g/m^3$  increase in  $PM_{2.5}$ , suggesting that long term exposure to  $PM_{2.5}$  is associated with increased risk of AD

## Conclusion:

This literature review have presented findings indicating that ambient air PM is associated with AD. The fine ( $PM_{2.5}$ ) and ultra-fine ( $PM_{0.1}$ ) particles seems to carry the greatest risk to the CNS. Individuals exposed to high levels of ambient air pollution experiences inflammatory responses and brain damage similar to AD, in frontal cortex, olfactory mucosa and olfactory bulb. Ambient air PM may reach the brain through either the nasal pathway or through the lungs via the systemic circulation. Small size PM may be able to reach the brain easily to produce oxidative stress by releasing cytokines. Ambient air PM may also be involved in producing ROS, which may result in formation of amyloid beta peptides and senile plaques surrounded by neurofibrillary tangles similar to AD. Since accumulation of amyloid-beta42 may be accelerated by air pollution, and exposure to ambient air PM are associated with impaired cognitive function, a plausible association exists between PM and AD.

Provided ambient air pollution is an etiologic factor, AD may at least partly be a preventable condition depending on the ability to reduce air



pollution, especially in heavy populated areas. More research is needed to learn more about the risk factors and mechanisms involved in the genesis of AD according to ambient air PM. If ambient air pollution is causally related to AD, the Public Health sectors need to work closely with communities, organizations, states and federal authorities to increase awareness of the problem, and to propose policy changes to minimize exposure.

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