The Trojan Horse Effect: An interdisciplinary review and recapitulation model of the correlation between Alzheimer’s disease and air pollution based on neurobiology, sociology of medicine, and eco-political science.

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Abstract: There has been emerging evidence that air pollution is a chronic source of neuroinflammation, which contributes to Alzheimer’s Disease (AD), an increasingly common and devastating illness in elderly populations. A report on the causal relationship between PM$_{2.5}$ from air pollution and AD provided scientific explanations for the mechanisms driving air pollution-induced CNS pathology, which stimulates calls for action at the political level. This review covers the scope of recognised and novel approaches associated with AD, highlighting how neurobiology, sociology of medicine and eco-politics collaborate to generate the interdisciplinary picture of the effects of PM$_{2.5}$ on this malignancy. More holistic and realistic views on the current approaches will allow this field to move forward and lead to an improvement to actionable policies.

Keywords: Neuroinflammation 1; Alzheimer’s disease 2; Air pollution 3; PM$_{2.5}$ 4; Eco-politics 5; Global trend 6; WHO Guideline 7; Recapitulation model 8.

1. Introduction

Whilst it has been well documented that individuals exposed to socially and economically disadvantaged conditions are likely to experience harmful physical and social environments more frequently than those in better social settings, compounding their disadvantages, studies on the interaction of these factors are limited [1]. Socially disadvantaged individuals, living in specific geographical areas due to their limited social and economic mobility, have historically experienced health disparities across their life span, compared to those in more socially advantageous circumstances [2]. Such conditions can interact to affect a wide range of environmental and biological processes that in turn influence health [3]. For example, exposure to harmful airborne pollution in the United States is correlated with social disadvantage, given that land and therefore property values decline noticeably near highways and industrial areas, which are major sources of airborne pollution [4]. Hence, socially disadvantaged individuals tend to be part of poorer communities who are often exposed to relatively high levels of airborne pollution [1].

This is important as exposure to air pollution - specifically particulate matter (PM$_{2.5}$) - was the 5th highest ranking health risk factor, accounting for 4.2 million deaths from lung cancer, respiratory infections, heart disease and chronic lung diseases according to data from HEI for global trends [5]. Inflammation, which can trigger not only the lung diseases but also the neurodegenerative diseases, is crucial for the biological mechanisms that relates air pollution to adverse health outcomes [6].
Among the many health impacts of inhaling airborne pollution, recent research has linked Alzheimer’s Disease (AD) which affects over 13 million people worldwide at a cost of more than £455 billion (US$600 billion) to airborne pollution [7,8]. Such pollution, exacerbated by human action, can be an important environmental factor to consider for AD, as it can be regarded as the most prevalent source of oxidative stress and environmentally stimulated neuro-inflammation, that we may confront in our daily lives [9].

The vast majority of previous studies on the causes of AD focus on other factors such as ageing, genetics and diabetes, because historical large-scale data on PM$_{2.5}$ exposure has been too scarce to investigate linkages that suggest airborne pollutants function as a trigger of AD [8]. Consequently, the most established risk factor for Alzheimer’s is aging as well as family history [8]. Interestingly, apolipoprotein E (APOE) ε4 and other loci confirmed in a genome-wide association study (GWAS) comprise less than 50% of heritable risk, which implies that genetics cannot necessarily be the major contributing factor [79]. Other known common risk factors include being a member of the female sex [10], head injury [11], cardiovascular disease [12], low educational level [13] and Downs syndrome [14]. Thus, it is important to explore the new hypothesis: that long-term PM$_{2.5}$ exposures may increase the risk for exacerbated worldwide cognitive decline and AD.

In this review, we integrate research from several disparate, but relevant fields –neuroscience, psychoneuroimmunology, environmental toxicology, and political and social science – in order to show how air pollution and particularly PM$_{2.5}$, can increase vulnerability to the development of AD. and hence reinforce the call from other health research that strategies to reduce atmospheric PM$_{2.5}$ need urgent implementation owing to the increased social and economic costs of AD. We firstly review studies illustrating the status of air pollution worldwide, and how different political frame works act to improve air quality. The paper aims to exemplify and categories the currently ongoing wide range of policies related to lowering PM$_{2.5}$ concentrations. Secondly, we summarise research linking PM$_{2.5}$ and AD. We examine toxicology studies based on the relationship between PM$_{2.5}$ and inflammation; and link this work to related studies on inflammation and AD. Thirdly, based on the literature, we propose an integrated, multi-level model of air pollution exposure, suggesting new appropriate daily life-style changes for individuals, and further roles that governments should play. We suggest the need for a more holistic approach to policy decision making, which can support sustainable economic activities and lead to co-benefits including positive health outcomes. Individuals with low social and economic status often tend to be part of communities which focus on economic activities rather than improving the environment, which can thus cause more potent inflammatory responses and potentially lead to increased risk of Alzheimer’s Disease, upon exposure to various harmful social and physical factors [15]. Lastly, we suggest possible future research.

Throughout the paper, we propose actions by which we can avoid the Trojan horse effect, “any disastrous result of an anticipated gain” [16].

2. Terminology

2.1. Alzheimer’s Disease (AD)

Alzheimer’s disease (AD) is the most common type of dementia, accounting for about 60-80% of cases [17]. Annual incidence is estimated at 0.6% for older persons aged 65-69, yet for those above 85, the incidence increases to 8.4% [18]. In terms of pathophysiology, AD generates generalised cortical atrophy, which appears mostly in the temporal lobes. AD is characterised by accumulation of extra and intracellular protein aggregates, extracellular deposits corresponding to amyloid plaques, which are formed by proteolytic cleavage of amyloid precursor protein (APP) by beta and gamma secretases [19,20,21,22].

2.2. Atmospheric air pollution and PM$_{2.5}$
Atmospheric air pollution can be defined as any biological, physical and chemical pollutant found in the air indoor or outdoor, which can alter the natural features of the atmosphere [23], as well as any substance which pollutes the atmosphere and cannot be absorbed through natural environmental cycles and flows, owing to its quantity and nature [24].

The World Health Organization (WHO) considers that the biggest environmental threat to health is air pollution [25]. Outdoor (ambient) air pollution is a combination of particulate and gaseous components, such as particulate matter (PM), sulfur dioxide (SO$_2$), nitric oxide (NO$_2$), ozone, lead, and carbon monoxide (CO), which are all known to have negative impacts on health [26]. Outdoor air pollution alone is estimated to cause 7 million deaths every year worldwide from diverse illnesses such as cardiovascular diseases, lung cancer (6%), and respiratory conditions (24%) [25]. Importantly, this mortality is mainly attributable to exposure to prominent airborne pollutant known as particulate matter (PM).

Size of PM ranges from wind-blown dust particles(<10µm) to ultrafine particles(>100nm), where their small size explains their biological impacts, as they are able to cross into the blood stream from the lungs and impact biological processes [28]. Being composite by nature, particle components often have toxic elements on their surface, e.g. polyaromatic hydrocarbons, which differ depending on the source of the PM, the season, and their geographical location. A great number of absorbed compounds on PM are known to be neurotoxic and also widespread [27,29].

Particles larger than 10µm in diameter get trapped in the upper airways, whereas smaller particles can be inhaled into the lungs. In general, granular particles are classified depending on their aerodynamic diameters: 2.5 to 10µm (PM$_{10}$), fine particles of less than or equal to 2.5µm aerodynamic diameter (PM$_{2.5}$), and ultrafine (UFPs/ UFPM) or nano-sized (NP) particles of less than or equal to 0.1µm [30,31].

PM$_{10}$ commonly originates from products of fossil fuel combustion, the internal combustion engine, road and agricultural dust, construction and demolition works, and brake wear emissions, and mining operations [30]. Likewise, the primary sources of anthropogenic PM$_{2.5}$ are metal processing facilities, oil refineries, brake emissions, residential fuel combustion, wild fires, power plants and tailpipe emissions [30]. In addition, both organic and inorganic compounds, such as sulphates, nitrates, carbon, lipopolysaccharide, ammonium, metals, hydrogen ions and water form PM$_{2.5}$ [9]. It is important to note that diesel exhaust particles (DEPs) are a main source among the ambient fine particles in urban environments [32]. The smaller fractions of PM (<2.5µm) can result in lung deposition and the penetration of the respiration tract, overall gaining access to the blood stream and nervous system [33].

The level of air pollution is associated with health and hence life expectancy as shown by a study where a decrease in ambient PM$_{2.5}$ levels across U.S. cities have been matched with a substantial increase in life expectancy, despite the changes in demographic and socioeconomic variables, for instance [34]. PM$_{2.5}$ concentration levels even below the national standards still demonstrated adverse effects, which were also shown to impact the socially disadvantaged individuals with low income or racial minorities the most [35]. In addition, they are exposed to worse air quality throughout their lifespan [26], which implies that socially disadvantaged individuals tend to be more vulnerable to air pollution, potentially leading to AD. Therefore, further studies are required to investigate how environmental and social factors interact on a larger scale (at global and national levels) in order to assess if and how synergy among such aspects triggers social disparities in health and greater vulnerability to AD. Understanding these interactions is fundamental for producing effective interventions and policies which can protect susceptible populations better, and in turn reduce health disparities, and the likelihood of AD.
3. Inflammatory Mechanisms Linking Air Pollution and Alzheimer’s Disease

Once PM is taken into the body, the smaller fractions rapidly enter the circulatory system, directly affecting the vascular system. When they are inhaled, they can penetrate through the alveolar-capillary barrier in the lungs, depending on several factors such as the particles’ size, chemical composition, charge and susceptibility to generate aggregates [36].

The large surface-to-volume ratio of small PMs can easily penetrate cell membranes and traverse the barriers in the brain and the lung. This ability to penetrate cell membranes explains how PM can enter neurons and erythrocytes [37]. Exchange of PM between PM-loaded erythrocytes and activated endothelial cells is possible due to the close contact between erythrocytes and endothelial cells [38].

PMs can enter the nervous system and have contact with the environmental air through a more direct route, which is the olfactory mucosa [39]. PMs can pass through the olfactory receptor neurons or trigeminal nerve, reaching the brain. Olfactory receptor neurons are known as bipolar sensory neurons, which mediate the sense of smell, by sending the sensory information from the nose to the central nervous system (CNS). While a layer of sustentacular cells covers the olfactory epithelium, olfactory sensory neurons can extend their dendrites through the mucous layer which covers the olfactory epithelium and interacts with odorants in the air directly. Through pinocytosis, receptor-mediated endocytosis and simple diffusion, nasally-inhaled pollutants can enter the cilia of olfactory receptor neurons and reach the olfactory mucosa [40]. As they incorporate into sensory neurons, they can be transported to the olfactory bulb through slow axonal transport along the axons [41]. From this point, the pollutants can be transported deeper into the CNS, along the mitral cell axons which project to various brain regions (such as the anterior olfactory nucleus, olfactory cortex, piriform cortex, hypothalamus and the amygdale) from the olfactory bulb [40].

Hence, PMs have been found in human olfactory bulb periglomerular neurons, as well as in the trigeminal ganglia capillaries [42]. Experiments on rats for controlled exposure to PMs and metals have also illustrated their accumulation in the olfactory bulb [43]. On the whole, these findings imply that the olfactory mucosa can directly take up MPs which can enter the CNS or cerebrospinal fluid through circumventing the circulatory system [27]. Uptake through the nasal route can be stronger due to the extra pollutant-induced systemic inflammation through weakening the olfactory mucosal barrier, which would lead to an enhanced neuropathology [40]. Ground-level ozone exposure triggers the CNS via the vagal nerves without involving the thoracic spinal nerves [44]. Toxicology research in humans and animal models argues that both local and systemic inflammation can be caused by the exposure to particle air pollution [45,46,47]. While the rate of PM translocation to secondary organs from their entry site is likely to be low, chronic and continuous exposure to MPs may contribute to a significant amount of accumulation in the brain as a secondary target organ [27].

Regardless of the route of entry, MPs can have a direct effect on the vascular endothelium cells when reaching the circulation by generating local oxidative stress or by triggering pro-inflammatory effects, resembling the lung tissue [42]. Inflammatory mediators released in the respiratory tract due to the chronic pollutant-induced epithelial and endothelial injury can result in systemic inflammation [48]. In addition, it is interesting to note that brain tissue samples collected from individuals from highly polluted regions illustrate a greater number of activated microglia, infiltrating monocytes, increased expression of IL-1β, endothelial cell activation, brain lesions in the prefrontal lobe, and Blood-brain barrier (BBB) damage [42].

4. Methodology

4.1. Framework

This paper illustrates how the World Health Organisation (WHO) considers air pollution, and to what extent each government responds to the phenomenon by examining the current political and
socio-economic policies that attempt to reduce such pollutants. In particular, BRIC countries (Brazil, Russia, India, and China), the EU, USA and UK will be investigated further from the case of the WHO, before drilling down into London (Figure 1), was an interesting case study due to the various economic activities, which co-exist with people’s understanding and attention towards environmental issues. Countries for investigation were selected based on their socio-economic status, given that “environmental protection as a priority stems from affluence” [49].

![Figure 1](image)

**Figure 1.** An inverted pyramid graph showing a top down approach of different regulatory government bodies for air pollution, illustrating the ways in which case studies are arranged in this chapter.

4.2. Sources of Evidence

Methodologically, it has been challenging to establish a causal relationship between environmental chemical exposures and AD. Patients usually do not know they have been exposed to particular chemicals above an acceptable level, and there are ongoing debates on the clarity of “acceptable” level of exposure to environmental chemicals for human health. Geographic location and the types of chemicals have both detailed and accurate enough to influence research data [50]. In addition, in terms of experiments, when assays of chemicals are implemented after diagnosis, residues may not correspond to exposure at the relevant time in life, thus hindering the aptitude to establish causality [51]. Thus, this paper often refers to the in vitro and in vivo studies carried out by Block & Calderón-Garcidueñas (2009), in order to establish a certitude that there is a causal relationship between PM$_{2.5}$ and Alzheimer’s disease. The acknowledgement that human epidemiologic studies in society have these limitations has resulted in the realisation that more sources for evidence are required. The assessment of cumulative and the corresponding reactions requires various tools and types of evidence in order to make rational and practical decisions for environmental health interventions and policies. This review illustrates the scope of what is known about air pollution and AD, followed by current understanding by political bodies of these associations. For additional detail, we implement other search methods.

4.2. Search Methods

We employed the framework defined earlier to commence a scoping search of the literature across the following disciplines: environmental sciences, eco-politics, immunology, and neuroscience. We searched the following electronic databases: Research Gate, Google Scholar, Science Direct, and PubMed. Grey literature examined included the UN, WHO, European Union, UK, USA, and some other government legislative and policy documents, technical data sheets and specifications, published textbooks, reports from NGOs, recognised websites (for example from construction organisations) and newspaper articles. We implemented the grey literature to identify further peer-reviewed studies. Using the framework domains, an initial set of keywords were developed.
4.3 Selection criteria and analysis

The search was not only limited to studies in English but also in other languages in order to understand the documents produced in those countries of research. The translation of other languages was conducted using recognised online translation. Any documents with irrelevant information to the scoping review and/or with different purposes, e.g. sales advertisements, unsubstantiated claims were ignored. We referred to the findings of included studies for grouping and characterising relationships between air pollution and AD.

5. Air pollution, Health and Current Political/ Socio-economical Situations

As the level of air pollution becomes more severe each year, as well as its effects on health and the environment, various organisations (including national governments, NGOs, WHO) began to produce guidelines for preventing air pollution in various contexts. However, different bodies maintain different standards and guidelines based on the regulations that the WHO has set, as each area’s main sources and components of air pollution are distinctive due to diverse socio-economic activities [52]. It is important to assess the extent to which these governmental bodies are taking actions for the improvement of the air quality, and if there have been other aspects prioritized over the environmental side, then it is also essential to evaluate whether there has been a reasonable intention to justify their weak policies towards the environmental improvement.

5.1 World Health Organisations

First released in 1987 and updated in 2005 (the document published in 2018 is still based on the 2005 version), the WHO air quality guidelines were produced to suggest a guidance in alleviating the health impacts of air pollution, based on current scientific evidence [25]. These guidelines, which specify targets for a wide range of policy options for air quality management, should be considered among policy-makers [52]. They are based on four common air pollutants: Ozone ($O_3$), sulphur dioxide ($SO_2$), nitrogen dioxide ($NO_2$), and particulate matter (PM) [25].

Air pollutant concentrations are assessed at specific monitoring sites, which when combined most represent the general population exposures [25]. Air pollution levels can be greater near particular sources of air pollution, including power plants, roads, and large stationary sources [53]; and thus, it is vital to apply special measures to lower the pollution levels to below the guideline values especially for the protection of populations residing in those environments. World Health Organization (2006) has constantly emphasised the WHO Air Quality guidelines as they believe that “it is possible to derive a quantitative relationship between the concentration of the pollutant (particulate matter and ozone) as monitored in ambient air and specific health outcomes”. These relationships are invaluable for health impact assessments and allow insights into the mortality and morbidity burdens from current levels of air pollution, as well as what health improvements could be expected under different air pollution reduction scenarios [52].

In addition to guideline values, interim targets have been set for each pollutant to enable a progressive decrease in air pollution in areas where pollution is extremely high. The focus for these targets is to assure a shift from high air pollutant concentrations to lower concentrations to prevent further serious and acute health consequences [52]. However, most of the established targets (Figure
1 and Figure 2) have not been met for the last ten years, which suggests new strategies are needed to reduce the pollution. For instance, until 2017, approximately 50,000 Britons still died each year from diseases induced by air pollutants, and six million working days are lost at a cost of £28bn per year due to pollution-related illnesses annually [54].

Table 1 WHO air quality guidelines and interim targets for particulate matter: Annual Mean Concentrations. (World Health Organization, 2016)

<table>
<thead>
<tr>
<th>Basis for the selected level</th>
<th>PM10 (µg/m³)</th>
<th>PM2.5 (µg/m³)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Interim target -1</td>
<td>70</td>
<td>35</td>
</tr>
<tr>
<td>Interim target – 2</td>
<td>50</td>
<td>25</td>
</tr>
<tr>
<td>Interim target – 3</td>
<td>30</td>
<td>15</td>
</tr>
<tr>
<td>Air quality guideline (AQG)</td>
<td>20</td>
<td>10</td>
</tr>
</tbody>
</table>

Table 2 WHO air quality guidelines and interim targets for particulate matter: 24-hour concentrations for management purposes. (World Health Organization, 2016).

<table>
<thead>
<tr>
<th>Basis for the selected level</th>
<th>PM10 (µg/m³)</th>
<th>PM2.5 (µg/m³)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Interim target -1</td>
<td>150</td>
<td>75</td>
</tr>
<tr>
<td>Interim target – 2</td>
<td>100</td>
<td>50</td>
</tr>
<tr>
<td>Interim target – 3</td>
<td>75</td>
<td>37.5</td>
</tr>
<tr>
<td>Air quality guideline (AQG)</td>
<td>50</td>
<td>25</td>
</tr>
</tbody>
</table>

The World Health Organization (2016) took PM measurements of certain cities for PM₁₀ or PM₂.₅ air pollution levels at global and regional levels, examining whether they meet or surpass the WHO Air Quality Guidelines annual mean values of 20µg/m³ for PM₂.₅. The sites were divided into high-, middle- and low-income countries within Africa, America, Eastern Mediterranean, Europe, South-East Asia, and Western Pacific [25]. According to World Health Organisation (2016), there were 16% of the assessed population who were globally exposed to the PM₁₀ or PM₂.₅ annual mean levels. These figures rise to 27% when the interim target 3 is applied (IT-3, 30µg/m³ for PM₁₀ and 15µg/m³ for PM₂.₅) of the AQG, 46% for IT-2, and 56% for IT-1.
Given that the global trend shows that improvement is required to meet the standards ensure that air quality has a lesser impact on the causation of AD, the BRICs were examined as were American, European, South-East Asian, and East Asian low/middle income countries.

5.2 BRICs

It is important to study the BRICs. With their currently large populations, increasingly influential positions in international politics and notable growth rates, the future of the global environment will rely hugely on their policies and practices [55]. In 2008, the four BRIC economies contributed to over one-third of global carbon emissions, not including the emissions from deforestation and other environmentally inadequate land use [56]. Since the BRICs comprise both developing and developed countries, they are left in a bind when attempting to balance the needs of their populations with environmental sustainability. Their stated priorities are to attract foreign investment, improve domestic industries and to educate the workforce in order to develop in a similar manner to Higher Income Countries (HICs) - Western Europe and the U.S., for example, where economic development is the primarily focus [56]. The BRICs are an important case for analysis, as there is a possible correlation between the socio-economic development and the likelihood of developing AD as less socio-economically developed communities tend to prioritise economic goals over environmental air quality which is linked with the potential development of AD. As Table 3 shows, substantial numbers of populations in the BRIC countries are exposed to high levels of PM$_{2.5}$ [57].

Table 3. Population exposed to PM$_{2.5}$ levels exceeding the WHO guideline value in 2015-2016 (Brauer, 2015).

<table>
<thead>
<tr>
<th>BRIC country</th>
<th>PM$_{2.5}$ air pollution, population exposed to levels exceeding WHO guideline value (% of total)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brazil</td>
<td>55.8</td>
</tr>
<tr>
<td>Russia</td>
<td>89.66</td>
</tr>
<tr>
<td>India</td>
<td>99.99</td>
</tr>
<tr>
<td>China</td>
<td>100</td>
</tr>
</tbody>
</table>

For Brazil, annual average PM$_{2.5}$ concentrations in 2015 were about 7-13µg/m$^3$ at ten monitoring sites in Rio de Janeiro, 22 µg/m$^3$ in Sao Paulo, and 7-28 µg/m$^3$ in six major cities near areas where high traffic volumes are expected [58]. The data illustrates that an estimated 40% of the Brazilian population live with air that contains a greater concentration of PM$_{2.5}$ than the WHO annual air quality guideline [58].

Air pollution leads to 49,000 deaths in Brazil every year, and about half of these deaths are accounted for by the outdoor pollution, particularly in cities [58]. However, the other 24,000 results from indoor air pollution, mainly due to cooking with solid fuels and wood, particularly affecting rural communities [59]. Air pollution levels in these households, almost 20 million people, are 10-15 times higher than in cities [58]. This value is 11-26 times greater than 10 µg/m$^3$ that WHO recommended. The government has set interim targets, which aim for 50% adoption of LPG (Liquefied petroleum gas) and improved cook stoves, estimated to save 7,350 lives per year [58].
The case is similar in India, where 8 out of 9 selected areas (Dheerur, Delhi, Pusa, Aya Nagar, Lodhi Rd, Noida, Mathura Road, and Pitamura) within India were exposed to PM$_{10}$ at a ‘critical’ level in 2014, and 7 areas (Dheerur, Mathura ROad, Delhi, Pusa, Lodhi Rad, Noida, and Pitampura) were also exposed to ‘critical’ air quality with an excessive level of PM$_{2.5}$[60]. The Delhi Pollution Control Committee (DPCC) identified that annual average PM$_{2.5}$ concentration should be cut down by 70% in Delhi to satisfy the annual standard of 40µg/m$^3$ as the data from 2014 to 2017showed that the concentrations were 132µg/m$^3$, 3 times higher than the annual safe standard [28]. Thus, EPCA (Environment Pollution Control Authority) has promoted bus rapid transit (BRT) or light rail transit (LRT) for NCR, a predominant ticketing system for a traffic clearance process in the city. Moreover, for non-motorised transport network, implementations of bicycle master plan and retrofitting roads have been advocated [28].

Likewise, air pollution became a more prominent environmental and political issue as the US Embassy in China started to publish its readings in 2008 on social media [61].

In 2013, 71 cities in China failed to meet the interim WHO target: Beijing, Tianjin and Hebei were advised to lower the PM$_{2.5}$ levels by 15%, 25%, and 25% respectively by 2017. However, experts believe that it would be difficult for Beijing to meet the target of 60µg/m$^3$ for the next few years although the average level in 2016 was 73µg/m$^3$ as Figure 2 depicts [61].

![Figure 2 PM2.5 levels in Beijing between 2013 and 2016, (source Chun,2017). Although meeting the 2018 target could be difficult, it may be achieved in the near future as Beijing is now in a better position with its improved economic structure, which means more direct action can be taken to tackle pollution.](image)

China’s Ministry of Environmental Protection (MEP) and Hebei, Tianjin and Beijing governments published air pollution measures to be taken in 2017 [61]. The report written by Chun (2017) included topics such as the use of coal stoves, popularizing public transport, and closure of unregistered industrial parks of polluting factories outside of the cities.

However, unlike the BRICs, which are on the verge of developed status, HICs show a different attitude towards protecting the environment. The United States and EU have been chosen as typical examples of HICs. The US National Plan to address AD was mandated by legislation enacted in 2011 in an attempt to reduce the chance of suffering from dementia by 2025.
5.3 European Union (EU)

Table 4 Air Quality Limit and Target Values, for PM10 and PM2.5 as given in the EU Ambient Air Quality Directive and WHO Air Quality Guidelines (Department for Environment Food & Rural Affairs, 2012)

<table>
<thead>
<tr>
<th>Size Fraction</th>
<th>Averaging period</th>
<th>EU Air Quality Directive (Objective and legal nature and concentration)</th>
<th>WHO guidelines</th>
</tr>
</thead>
<tbody>
<tr>
<td>PM10</td>
<td>1 day</td>
<td>Limit value: 50 µg/m³</td>
<td>50 µg/m³</td>
</tr>
<tr>
<td>PM10</td>
<td>Calendar year</td>
<td>Limit value: 40 µg/m³</td>
<td>20 µg/m³</td>
</tr>
<tr>
<td>PM2.5</td>
<td>1 day</td>
<td>25 µg/m³</td>
<td>25 µg/m³</td>
</tr>
<tr>
<td>PM2.5</td>
<td>Calendar year</td>
<td>25 µg/m³</td>
<td>10 µg/m³</td>
</tr>
</tbody>
</table>

In addition, the EU limit values (as shown in Table 4) follow EU parameters, which must not be exceeded and have been made compulsory by EU Directives to take all necessary measures to maintain the set values. Figure 3 illustrates that a majority of the EU countries succeeded in keeping their PM concentrations below the EU target values, although they still exceed the WHO guidelines.

Figure 3 A graph showing PM2.5 concentrations in relation to the target value in 2014. Each country has been given the lowest, median, and highest values at the stations, with the box plots representing the 25th and 75th percentiles. The red line shows the target value set by EU legislation, and the blue line represents the WHO standard. Image taken from European Environment Agency (2016).

Figure 3 shows a decrease in PM2.5 concentrations on average between 2006 and 2014. The trends of PM2.5 concentrations have a consistent pattern: while the small changes of PM2.5 level is found in rural areas, the largest average change can be found at industrial and traffic stations. Although
several countries have shown an increase in PM$_{2.5}$ annual mean concentrations at more than one station type in the same period, it is hard to find a statistically significant trend in most of the stations. It is difficult to draw firm conclusions from the trend indicated in the data, but it is clear that there is reduction in PM$_{2.5}$ concentrations in general, which is a positive sign in terms of the association with AD as well. Interestingly, Figure 3 shows that HICs, located in the west of Europe, have generally lower concentrations of PM$_{2.5}$, while countries with lower Gross Domestic Product (GDP) in the east have higher concentrations [62]. This confirms that there is a relationship between economic activities and the PM concentrations, which suggests that it would be difficult to force all the countries to follow the PM guideline values, as it is inevitable for some Lower Income Countries (LICs) to limit their activities regarding PM concentrations. Additionally, while HICs can afford greater investment in developing AD treatment as well as well-being care for the patients, it is difficult for LICs, which already show a greater level of PM (implying a greater likelihood of developing AD), to improve their service to look after the patients with limited governmental funding available.

5.4 London

Drilling down from cases of BRICs and the EU, London is a particularly significant area of investigation. London is a post-industrial city and people have been concerned about the environment for a long time. However, despite their concerns in environment, people tend to support and follow opinions which benefit them based on their agenda – which is why environmental policies still need to be reinforced further. Furthermore, the recent event, Brexit, may affect the regulation of PM level in London as it may impact the current obligation to follow the EU standards.

With the increasing population growth and rapid urbanization, London has been recognized as one of the busiest cities in the world. Such urbanization has exposed people to heavy traffic flow; and growing rates of dementia are associated with the traffic situation in London, given that AD risk diminished as people resided farther from roads. 7% of dementia risk increased by living within 50 metres, 4% at 50-100 metres and 2% at 101-200 meters [63]. There was no increase after 200 meters [63]. It is important to also note that housing price decreases nearer to main roads. Traffic emissions account globally for 25% of ambient PM$_{2.5}$ [64].

The London Mayor announced that central London established a £10 charge for vehicles that do not satisfy Euro 4 standards when entering the area from October [65]. Along with T-charge, online application was implemented for the drivers to check their vehicles. Additionally, there have been 12 low-emission bus zones across the city where electric and hybrid buses can only be operated [65]. The use of bicycles has been advocated among the general population, however, there has been debate as bike lanes augment traffic congestion, and thus air pollution. In the areas exceeding legal air quality, 440 schools will distribute air filter masks to students [65].

6. An integrated multi-level model of early life stress, air pollution, and health

In undertaking this study, the following has been established – PM$_{2.5}$ exposures can result in AD due to the neuro-inflammatory responses, and the increased likelihood of developing AD due to PM$_{2.5}$ can be greater among the relatively less socio-economically developed communities, who are more likely to be exposed to environments where economic activities are prioritised over the air quality improvement. It is suggested that due to a lack of understanding of the impacts on AD, public health organisations may be underestimating the already substantial health burden and health care costs related to air pollution [66]. It is also noted that the latest assessment of the global burden of
disease caused by PM$_{2.5}$ conducted by WHO, does not include AD [66]. Perhaps, such low emphasis is driven in part by a focus that prioritises economic development over health impacts, particularly in LICs. Air pollution levels are significantly greater in the BRICs and other developing countries compared to U.S. and EU levels [66]. Given that there is a link between air pollution and Alzheimer’s disease, we propose an integrated, multi-level model of the interactions between air pollution, socio-economic development, and Alzheimer’s disease, as shown in Figure 4.

![Figure 4](image_url)

Figure 4 The model depicts a pathway through which specific socio-economic factors (poor residential conditions and geographical sites) and environmental factors (i.e. air pollution exposure) interact to increase the risk of developing Alzheimer’s Disease. The X-axis represents the degree of socio-economic development, which can be applied for any scales, ranging from the household income to the national scale. The Y-axis shows the PM$_{2.5}$ prevalence in percentage. The blue circles indicate the likelihood of developing AD, which correlates to the relationship between the socio-economic development and PM$_{2.5}$ prevalence. First, socio-economically disadvantaged individuals are turned out to be at higher risk for poor health, compared to those in better living conditions, due to greater likelihood of living by the lower-price housing areas and greater exposure to air pollution, and other inflammation-inducing causes over the lifetime. The graph suggests that the lower the socio-economic development, the higher the chance of being exposed to the PM$_{2.5}$, which can thus result in a greater likelihood of developing AD.

As depicted in Figure 4, the model underscores why socially disadvantaged individuals are at a particularly high risk of experiencing more inflammation-related health problems, especially Alzheimer’s disease, compared to individuals in socially advantageous circumstances.

We also discuss direct investment in finding cures for AD or fighting against air pollution – especially the relation to particulate matter. Three points have been developed throughout: 1) combatting air pollution is more likely to draw political attention, 2) applying wide-ranging environmental regulations to developing economies may lead to some economic and social inequities relative to HICs, 3) There is moral hazard to be considered for less economically developed countries. The conclusion of this argument points towards the development of AD cures being a more suited approach, despite approaching the problem through simultaneous measures being necessary.
6.1 Combatting air pollution is more likely to draw political attention

Before discussing which of the two approaches should be prioritized, it is reasonable to examine ongoing efforts on both investment on AD cures and the investments on combatting air pollution. For the development of AD cures, the currently available treatments include drugs, which lessen the symptoms of AD or slow down the progression of developing the illness. The main medication available are acetylcholinesterase inhibitors and NMDA receptor antagonists, which restore lowered levels of acetylcholine. This helps to convey messages between certain nerve cells and inhibit the hypofunction of N-Methyl-D-aspartate receptor that can cause memory deficits [17]. However, treatments can only help manage the disease rather than eliminating it altogether. Although there is no current cure for AD, it is suggested that the first drug may be available within 4 years [68]. Currently, Liraglutide, mainly used to treat diabetes by binding to the same receptors, as does endogenous metabolic hormone GLP-1 to stimulate insulin secretion, can help stop AD’s advancement and boost mental function [68].

Compared to the number of people suffering from AD and its cost of care, investment for AD research is significantly low. For example, the total UK government and charitable funding on research into AD in 2012 was £90million [69], and while the US government spends $200billion on AD care, it spends less than 1% of that figure on research [70]. This could explain the slow development of medications, despite AD continuing to be the World’s 6th leading cause of death [71].

Countries generally spend a relatively larger sum in tackling environmental issues. For example, in the first quarter of the UK government’s release of budget allocation 2017, the Environment, Food and Rural Affairs department was allocated £0.7billion out of the £46.2 billion public sector gross investment [72]. The health sector’s estimate was £4.6 billion, but the specific allocation provided was heavily concentrated on NHS insurance, rather than research investment [72]. This is a common phenomenon as the environmental agenda is more likely to attract wider political attention compared to developing treatments for specific diseases, if they are not perceived as important. With particulate matter becoming recognised as a serious issue, countries show a higher tendency to develop related policies, e.g. South Korea where a majority of candidates in the 2017 election specifically mentioned ‘particulate matter’ as a problem to be addressed. Due to the topic being linked to a wider spectrum of public interest, developing solutions to air pollution is far more likely to receive political (and economic) support from governments, than AD research. We suggest that the importance of investing in the development of AD cures should be highlighted with links to PM made explicit.

6.2 Environmental regulations may lead to economic and social drawbacks

Following from the current reactions towards developing cures for AD above, it is proposed that a socio-economic understanding of the consequences of AD is necessary [69]. However, this is ambitious as there is no magic bullet for prevention. Rather than expensive anti-aging pills and repeated memory games, a more pragmatic approach may be required. Even if all the PM in the air could be eliminated, there are still a variety of other factors that lead to AD. Such factors, as related above entail possible economic and social drawbacks and need to be tackled through clear regulations. Pragmatically, investing more to the research supporting the development of cure will be more meaningful in the long-term since addressing the multiple factors contributing to the onset of AD would be very difficult, and because investment is currently lacking as previously mentioned.

The world would be evidently better if all countries adhered to strict environmental policies. However, this is not realistic - limiting economic activities may prevent deaths from developing AD through lowering the PM concentrations, but it will have an effect on the lifestyles of individuals and
the performance of firms, resulting in serious societal consequences. For example, limiting China’s huge capital iron and steel works, a primary source of pollution, could cost 40,000 jobs [73]. Moreover, China’s economic progress is firmly powered by cheap coal, despite its contribution to the PM$_{2.5}$ concentration level. Coal combustion contributes 40% to the total national level and up to 50% in Sichuan Basin [74]. The equal application of rigorous environmental policies would generate huge obstacles to economic growth and a risk to political stability, although it would be disingenuous to suggest that the Chinese government is not aware of this and starting to take steps to address these issues.

Despite these potential drawbacks, the clear benefit of preventing air pollution for human health should not be neglected. The annual costs of air pollution related mortality for long-term exposure to PM are projected to be £1.4 billion per year in London, with an additional £14 million for respiratory hospital admissions and £5 million for cardiovascular hospital admissions [75]. Further investment in tackling air pollution would reduce healthcare costs as a decrease in PM$_{2.5}$ will provide benefits related to health in general. Along with the data shown above regarding the economic burden of AD, the US Environmental Protection Agency (EPA) has estimated that through the Clean Air Act, (US) $2trillion can be saved by 2020 through the prevention of further deaths and illnesses caused by air pollution [66]. However, such benefits are not specific to AD but also to other illnesses, implying that in the light of AD prevention and cure, the approach is overly broad. The comparison of socio-economic effects of the two approaches clearly show that while considerable amount of benefits exists in reducing air pollution, direct investment to research is a more preferable approach.

6.3 Moral hazard for developing countries

Even if we were to assume that AD was solely caused by air pollution, a focus on the reduction of PM$_{2.5}$ would not be an adequate solution due to socio-economic elements. This is due to the ethical issue on whether it is fair to impose over tight environmental regulations to countries who have not yet benefitted from industrialization. It is often argued that it is hypocritical for HICs to demand LICs to prioritise environmental protection. Ultimately, this issue arose in part as HICs damaged their environment through industrialization [67]. In any case, as they become more affluent, they seem become more aware of the environment and come to the position where they can afford investment to prevent further release of PM$_{2.5}$, as argued by Becker (2013) that “environmental protection as a priority stems from affluence.” The EU and America already pose high tariffs on products made cheaply in LICs, which are sold in Europe or the USA. Limiting the development of profitable yet polluting industries, such as oil refineries and steel, can force these countries to remain economically backwards [67].

This is especially true since there are still many ways in which HICs can contribute to the problem of PM without significantly affecting themselves socio-economically. Without fully implementing such measures, it would appear inequitable to apply tighter standards to LICs. For instance, China can still use coal with a significantly lowered rate of PM$_{2.5}$ release by controlling its emission during and after its combustion. Firstly, the optimization of combustion temperature, burning time, and boiler load can lower the emission of fine PM [76]. Secondly, fabric filters (FF) and electrostatic precipitators (ESP) are the two most widely applied conventional particulate emission control devices [77]. ESPs can collect 98% of PM$_{2.5}$ when combined with flue gas desulphurisation (FGD) and/or other pollutant control systems, and FFs have a higher collection efficiency – up to ~99.7% for PM$_{2.5}$ [77].

Such measures can positively impact the health of the citizens of the respective countries, which makes HICs forcing LICs to act even more ironic. This is because they themselves maybe neglecting room for improvement. Since there is already much space for improvement that can be made without
tight regulations in LICs by HICs, prioritising regulation globally in the course of preventing AD is not an ideal approach, especially because it would be very unfair for developing nations to be forced to give up the social benefits from environmental exploitation. By lessening the maximum outdoor PM$_{2.5}$ exposure to 15µg/m$^3$, 7000 lives can be saved in Brazil. In Latin America, where firewood was mainly used for cooking in households, the mean annual exposure in Latin America and Caribbean concentration of PM$_{2.5}$ reached approximately 23µg/m$^3$ in 2000 [78]. Even though it has been reduced to 17.67µg/m$^3$ in 2016, it is still higher than the WHO’s recommended level [58,78]. This can be prevented through the simple resolution of cook stoves with chimneys which vent to the outside, cutting down the exposure by over half, and reducing the risk of disease and death by approximately 34%. Adopting LPG, which is a slightly more expensive option, can reduce the disease and death by 47-67% [58]. Economically, although adopting such methods could initially cost 1.7 billion Reals per year, reaching the final target can provide annual benefits of 6.3 billion Reals [58]. This is more than twice the benefits of adopting LPG stoves, as it will avoid community pollution leading to possible diseases, including AD. Since there is already much room for needed improvement without tight regulations, prioritizing regulation globally in the course of preventing AD is an impractical approach, especially as it could negatively impact the developing nations.

7. Limitations

It is inevitable that this paper does bear some limitations. Firstly, PM$_{10}$ values were used when PM$_{2.5}$ values were not available. Thus, the analysis of data and severity may have been underestimated and inconsistent; because the effect of PM$_{2.5}$ is more detrimental than that of PM$_{10}$ in the light of inducing Alzheimer’s disease. Secondly, since the conclusions have been arrived at by collecting data conducted through different measurement techniques and locations, the estimated pattern of PM$_{2.5}$ over time and extrapolating levels beyond the available sampling data has limitations. Therefore, the more efficient and direct ways of improving policies could have been suggested through the inspection of statistical and quantitative data, which was difficult to conduct due to the data available. In addition, for future work, a simulation of economic growth in dynamic framework is required, including emissions and abatement policies of toxic air pollutants, specifically PM$_{2.5}$. This will be able to provide a potentially more precise representation of effectiveness of prevention policies in reducing the risk of AD through statistical quantitative research. However, the authors feel that even despite the limitations of this work, there are potential lessons for guidance for policy makers.

8. Concluding Remarks and Future Perspectives

Alzheimer’s disease is an illness which may become both preventable and curable. Throughout the paper, it has been shown that air pollution is one of the leading factors of developing AD through increasing the levels of microglia, monocytes, IL-1β, and endothelial cell activation, resulting in a disruption of the BBB and neuro-inflammation. Furthermore, olfactory mucosa is the direct route through which PMs can enter the nervous system. By pinocytosis, receptor-mediated endocytosis and simple diffusion take place, leading to neuroinflammation which is associated with an increased chance of Alzheimer’s disease. We have attempted to find a means of alleviating the risk induced by this link, with minimal repercussions to various groups of individuals with different agendas in society.

We suggest that direct investment for more research should be prioritized, but it does not diminish the importance of reducing air pollution as a means for reducing the occurrence of AD. Despite favouring direct investments, it is important to note that we should not neglect of combating...
air pollution when discussing AD treatments and cures. The third point discusses the effectiveness of the approach, and it should be clear that such measures should be implemented simultaneously if at all possible, because of the cost-effectiveness. We anticipate a negative multiplier effect if we do not pay more attention to prevention. Once the cost for dealing with air pollution increases, it is suggested that governments should budget to increase investment to compensate. However, this leaves less budget to invest into potential business markets and welfare, which may slow down the economic growth and lower the welfare standard. Ultimately, this may lead to a lower labour force due to less education and access to health care. These consequences may help to explain government hesitance in investment and need to be considered before financing the development of AD medication.

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