

## The Trojan Effect: Would prevention of air pollution be a better solution to Alzheimer's disease than developing medication?

### Efekt konia trojańskiego: Czy przeciwdziałanie zanieczyszczeniu powietrza przyniosłoby lepsze skutki w walce z chorobą Alzheimera niż badania nad wynalezieniem leku?

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#### ABSTRACT

Emerging evidence is showing that air pollution is a chronic source of neuroinflammation, which has a causal relationship with Alzheimer's disease (AD), an increasingly common and devastating illness in elderly populations. A report on the association between PM 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 scoping review considers the range of recognised and no-

vel approaches associated with AD, highlighting how neurobiology, sociology of medicine and eco-politics collaborate to generate the interdisciplinary picture of the effects of PM on this malignancy. Such holistic approaches will allow this field to move forward and could lead to an improvement of actionable policies.

**Keywords:** air pollution; PM2.5; WHO Guideline, neuroinflammation; Alzheimer's disease; eco-politics; global trend; recapitulation model.

#### INTRODUCTION

Exposure to air pollution has been 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 Health Effects Institute (HEI) for global trends in 2017 [1]. Recent findings have

suggested that air pollution may raise the chance of developing Alzheimer's disease, with new evidence that the health of individuals of all ages is at risk from living with polluted air. Alzheimer's disease (AD) affects over 13 million people worldwide at a cost of more than £455 billion (\$600 billion US) to airborne pollution [2, 3]. 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 [4]. Although an observational study in BMJ Open established that air pollution cannot be the only direct cause of the dementia cases, higher levels of Alzheimer's disease diagnosis could not be explained solely with other factors known to increase risks of the disease [5]. It is stated that there is accumulating knowledge adding air pollution to the list of risk factors for AD [6]. Their calculations suggest that it elevates risk by 7%, suggesting approximately 60,000 of the total 850,000 AD cases in the UK, in mathematical terms [6].

One of the potentially fatal air pollution components is particulate matter (PM). PM, which could be particles in varying sizes, refers to condensed phases suspended in the atmosphere. PM, including molecules, radicals, atoms, and precipitations, is mostly observed near the surface [7]. A number of absorbed compounds on PM are known to be neurotoxic and also widespread [8,9]. Being composite by nature, toxic elements on their surface, e.g. polycyclic aromatic hydrocarbons, vary depending on the source of the PM, its geographical location and the season. Size of PM ranges from wind-blown dust particles ( $<10\mu\text{m}$ ) to ultrafine particles ( $>100\text{nm}$ ), where their small size accounts for their biological impacts, as they are able to cross into the blood stream from the lungs and impact biological processes [10]. The smaller fractions of PM ( $<2.5\mu\text{m}$ ) known as PM<sub>2.5</sub> as well as ultrafine particles can result in lung deposition and the penetration of the respiratory tract, gaining access to the blood stream and nervous system [11]. Neuro-inflammation can also be triggered by these particles, which can eventually cause AD [4].

Previous studies on the causes of AD focus on other factors such as ageing, genetics and diabetes, because historical large-scale data on PM<sub>2.5</sub> exposure has been too scarce to investigate linkages that suggest airborne pollutants function as a trigger of AD [2]. Thus, it is important to explore a new hypothesis: that long-term PM<sub>2.5</sub> exposures may increase the risk for exacerbated worldwide cognitive decline and AD. Research has highlighted PM<sub>2.5</sub> as having a stronger link with the risk of developing AD compared to other air pollution components because of its small size and surface and components [12]. Therefore, PM<sub>2.5</sub> is the particular focus of this study.

In this review, we integrate research from several disparate, but relevant fields including neuroscience,

psychoneuroimmunology, environmental toxicology, and political and social science in order to show how air pollution and particularly PM<sub>2.5</sub>, can increase vulnerability to the development of AD. In doing this, we reinforce the call from other health research that strategies to reduce concentration PM in the ambient air need urgent implementation due to the increased social and economic costs of AD. 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 in less socio-economically developed communities show propensity in their primary focus on economic activities, rather than improvements in the environment; this 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 [13]. Throughout the paper, we propose actions by which we can avoid the Trojan horse effect, "*any disastrous result of an anticipated gain*" [57].

## EPIDEMIOLOGICAL EVIDENCE OF THE ASSOCIATION OF AIR POLLUTION AND ALZHEIMER'S DISEASE

Since major accidents during the 20th century, such as the 1952 London Great Smog event, the exposure to polluted air and particulates aroused heated arguments, and revealed their association with chronic illnesses, such as cardiopulmonary morbidity [15, 16]. For example, one recent epidemiological research conducted in 10 European cities suggested that near road traffic-related pollution causes chronic disease, as well as exacerbation of related pathologies; exposure to road traffic-related pollution accounting for 15% of all episodes of asthma cases, and similar patterns for coronary heart diseases in older adults [17].

It is only recent that epidemiological studies have started to realise the correlation between air pollution and accelerated cognitive decline and AD [18]. There has been a list of animal models which demonstrated significant values of the lethal effect of PM on the CNS (Table I).

Adults exposed to polluted air may undergo accelerated cognitive impairment. In China, Mexico and the U.S., elderly residents over 65 years old who reside in areas with high air pollution generally performed at a significantly lower level on a mini-mental state examination (MMSE), one of common cognitive examinations to evaluate AD, than those in

**Table I.** Experiments with animal models to show the correlation between cognitive impairment and air pollution**Tabela I.** Eksperymenty na modelach zwierzęcych pokazujące korelację pomiędzy zaburzeniami poznawczymi a zanieczyszczeniem powietrza

Year	Model	Findings	Citation
2002	Mongrel dogs	Elevated Nf-kB, iNOS, NFTs, non-neuritic plaques, and neuronal morphology changes in Mexico city animals.	[28]
2003	Mongrel dogs	Elevated Nf-kB, iNOS, COX2, Ab plaques, APP expression, and AP DNA sites in Mexico City animals.	[29]
2005	BALB/c mice	Whole brain Nf-kB, IL-1a up in both PM2.5 and UF exposures, TNF-a only significantly elevated in PM2.5 exposure.	[30]
2008	Mongrel dogs	Elevated COX2, IL-1b, GFAP, and white matter lesions in Mexico City animals	[31]
2008	APOE / C57BL/ 6J mice	Whole brain AP1 elevate with both exposures, NFKB solely with high exposure. GFAP level and pJNK to JNK ratio elevated in low exposure only	[32]
2008	BALB/c mice	Elevated escape latency in MWM. Elevated GluN1, GluN2A, GluN2B, IL-1b, and TNF-a mRNA in the hippocampus	
2010	Fischer F344/ DUCRL rats	TNF-a, IL-1b elevate in the striatum. No Nf-kB change.	[34]
2010	Wistar rats	Reduced SOD and MDA in animals treated both pre and postnatally. tGSH reduced in PND21 to adulthood group only. Reduced performance in spontaneous nonmatching-to-sample recognition test for continuous exposure and PND21 to adulthood.	[35]
2011	C57BL/6J mice	Reduced learning ability and memory in Barnes maze task, reduced time in open maze center, and elevated depressive response in forced swim test. Reduced spine density and dendrite length in the CA1. IL-1b, TNF-a, and HO1 expression elevated in the hippocampus.	[36]
2011	SpragueDawley rats	TNF-a elevate in olfactory bulb, midbrain, frontal lobe, temporal lobe in highest treatment, with 311 mg/m <sup>3</sup> treatment elevated in midbrain. IL-1b, a-synuclein elevated in midbrain with highest exposure, along with a-synuclein, MIP-1a down. Ab-42 and tau elevated in frontal lobe with highest exposure.	[37]
2011	C57BL/6J mice	GluR1 reduce and elevate in CD14, CD68, GFAP, IL-1b, and IL-6 in the hippocampus.	[38]
2012	FVBN mice	Aβ-load elevated.	[39]
2013	C57BL/6J mice	Elevated fixed ration operant wait time, no change in locomotor behaviors.	[40]
2013	Spraguee Dawley rats	HO-1 and SOD2 mRNA elevated in multiple brain regions with all exposures. Nrf-2, IL-1b, and TNF-a elevated in striatum and hippocampus solely with UF PM. Nf-kB increased in striatum with UF PM.	[41]
2014	C57BL/6J mice	Ventriculomegaly in males. Reduced GFAP in males, elevated GFAP in PND14 females. Elevated IBA1 in males. Variable changes in neurotransmitters and cytokines based on sex and brain region	[40]
2014	C57BL/6J mice	Reduced NOR test performance with early exposure. Variable neurotransmitter changes based on sex, region, and treatment	
2015	C57BL/6J mice	Temporal Cortex AB load elevated in 39 week treatment, APP reduced, BACE elevated, no change in tau load. PSD95 elevated in both treatments. Cytokine assay exhibited elevate in chemoattractants, but not IL-1b, IL-6, or TNF-a. No change in GFAP, VCAM, IBA1. Cox1 and Cox2 elevated	[42]
2015	Wistar rats	With highest exposure, IL-6, IL-1b elevated with highest exposure in temporal lobe, COX2 elevated the in midbrain and temporal lobe, and TNF-a and Ab-42 elevated in multiple brain tissues. DNA damage, ROS, and H2O2 elevates observed in frontal, temporal lobes.	[43]
2017	5xFAD ± APOE 33 or 34, and C57BL/6J mice	Elevate in Ab protein load in APOE 34 Cerebral Cortex. Lowered CA1 neuron density in wild type and APOE 33. GluR1 reduced in all models.	[23]

less polluted area [19]. PM<sub>2.5</sub> [20] has been shown to be particularly related to poor performance on MMSE among the elderly.

One Canadian study showed a positive causal relationship between fine particulate matter exposure and dementia incidences for about 2.1 million older adults living in Ontario [21]. Finch found a similar association between exposure to airborne particulate matter and cognitive impairment in 3,647 women aged between 65 and 79 years old across 48 states in the US and that living with fine particulate matter in excess of the annual EPA standards (12 µg/m<sup>3</sup> based on the EPA's finalized update in 2012 [22]) was associated with an increased chance of global cognitive decline and all-cause dementia, by 81% and 92% respectively [23].

A Taiwanese study followed 871 people over 10 years to confirm the association between AD and air pollution such as PM<sub>10</sub> [24]. The research showed an increase of AD risk by 4.17 in the PM<sub>10</sub> concentrations [25]. Another recent study from China which found a substantial reduction in intelligence also related to breathing polluted air, equivalent to losing a year of education [26].

More emphasised importance on this association eventually led to several more studies on a larger scale in Europe, focussing on traffic-related air pollution and the risk of developing AD. A study by Carey et al. estimated the air and noise pollution levels across London, linking to 131,000 patient health records of 50–75-year olds, within M25 main traffic motor way. Their health was tracked from 2005–2013, with 1.7% of the patients showed symptoms of dementia [6]. There is also data on AD incidence over a 15-year period obtained from the longitudinal Betula study, where traffic air pollution exposure was evaluated using a land-use regression model with a spatial resolution of 50 m × 50 m [27]. Out of 1,806 participants, 191 were diagnosed with AD during follow-up, and 111 were diagnosed with vascular dementia. Participants in the group with the highest exposure to traffic-caused air pollution showed a tendency towards a higher chance to be diagnosed with dementia (AD or vascular dementia), with a hazard ratio of 1.43 [27].

### **INFLAMMATORY MECHANISMS LINKING AIR POLLUTION AND ALZHEIMER'S DISEASE**

Once ultrafine PM is taken into the body, the smallest 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 particle size, chemical composition, charge and susceptibility to generate aggregates [44]. The large surface-to-volume ratio of smaller PM can 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 [45]. Exchange of PM between PM-loaded erythrocytes and activated endothelial cells is possible due to the close contact between erythrocytes and endothelial cells [46].

PM can enter the nervous system and have contact with the environmental air through a more direct route via olfactory mucosa [46]. PM can pass through the olfactory receptor neurons or trigeminal nerve, reaching the brain. Olfactory receptor neurons (known as bipolar sensory neurons) 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 directly with odorants in the air. Through pinocytosis, receptor-mediated endocytosis and simple diffusion, nasally-inhaled pollutants can enter the cilia of olfactory receptor neurons and reach the olfactory mucosa [47]. As they incorporate into sensory neurons, they can be transported to the olfactory bulb through slow axonal transport along the axons [47]. 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 [47].

Hence, PM and its components have been found in human olfactory bulb periglomerular neurons, as well as in the trigeminal ganglia capillaries [31]. Experiments on rats for controlled exposure to PMs and metals have also illustrated accumulation in the olfactory bulb [48]. On the whole, these findings imply that the olfactory mucosa can directly take up PM which can enter the CNS or cerebrospinal fluid through circumventing the circulatory system [9]. Uptake through the nasal route can be stronger due to the extra pollutant-induced systemic inflammation which can be executed through weakening the olfactory mucosal barrier, which would lead to an enhanced neuropathology [31].

Regardless of the route of entry, PM 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 [48]. Inflammatory mediators released in the respiratory tract due to the chronic pollutant-induced epithelial and endothelial injury can result in systemic inflammation [49]. PM consists of bacterial lipopolysaccharide (LPS) and combustion-derived metals such as vanadium and nickel, which are the agents able to evoke inflammatory responses [29, 50, 51]. Ultrafine PM induces severe inflammation when deposited in the lung [52]. Previous studies have been successful in showing the inflammatory process in the upper and lower respiratory tract of human and dog residents of Mexico City [29, 53].

Systemic inflammation can be noticed in the brain. The research conducted by Calderón-Garcidúe et al. and previous studies have provided evidence of brain inflammation in the form of an up-regulation of COX2 expression, which is predominantly noticed in capillary endothelium, in the brains of both human and animals [29]. Chronic respiratory tract inflammation may result in chronic brain inflammation by changing degrees of circulating cytokines, such as TNF- $\alpha$  and IL-1 $\beta$ , which are able to evoke expression of inflammatory mediator genes – COX2, which is an extremely potent biologically active mediator of inflammation – within brain capillary endothelium [54]. A positive correlation between COX2 mRNA and AP sites in frontal cortex has been observed by Calderón-Garcidúe as a possible outcome of COX2-mediated prostanoid synthesis, a primary source of reactive oxygen species capable of impairing DNA [55].

Recently it has been found that an increase in soluble Amyloid-beta (A $\beta$ 42) is the causative factor of AD [56]. A plaque deposition and neurofibrillary tangles in AD stem from intraneuronal A $\beta$ 42 accumulation in target areas [56]. Both an up-regulation of COX2 expression and the accumulation of A $\beta$ 42 were observed in the high PM exposure group [55]. It is plausible that A $\beta$ 42 accumulation may be a result of the increase in COX2 expression. According to a pathology observation in the subjects chronically exposed to severe level of PM, their pathology was very similar to the usual pathology of developing AD [55]. The A $\beta$ 42 accumulation from the high exposure of PM may also be an indication of AD pathogenesis preceding the development of neurofibrillary tangles and A $\beta$  plaques [55].

## AIR POLLUTION, HEALTH AND CURRENT POLITICAL, SOCIO-ECONOMICAL SITUATIONS

As the level of air pollution becomes more serious each year, as well as its detrimental effects on both health and the environment, various governmental bodies, including national governments, NGOs, and the World Health Organisation (WHO) began to produce guidelines for lowering PM levels in various contexts. This document illustrates how the World Health Organization (WHO) is considering air pollution and to what extent each government responds to this phenomenon by analyzing the current political and socio-economic policies that are trying to reduce such pollution. In particular, the BRIC countries (Brazil, Russia, India and China), EU, and London will be further compared with WHO recommendations due to different types of economic activities that coexist with people's understanding and attention to issues environmental. Countries for investigation were selected for study based on their socio-economic status, given that “*environmental protection as a priority stems from affluence*” [57].

### World Health Organisations

The WHO air quality guidelines – first released in 1987 and updated in 2005 (the document published in 2018 is still based on the 2005 version) – were produced on the basis of current scientific evidence, considering four common air pollutants ozone (O<sub>3</sub>), sulphur dioxide (SO<sub>2</sub>), nitrogen dioxide (NO<sub>2</sub>), and particulate matter (PM) [58].

Air pollutant concentrations are assessed at specific monitoring sites, which when combined can represent the general population exposure in a given area [58]. Air pollution levels can be greater near sources of air pollution, including power plants, roads, and large stationary sources such as industrial facilities [59]. It is vital to apply mitigation measures to lower the pollution levels to below the guideline values especially for the protection of populations residing in those environments. WHO (2006) has constantly emphasized the air quality guidelines as they believe that, it is possible to derive a quantitative relationship between the concentration of the pollutant (e.g. particulate matter) 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 [60].

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 of these targets is a shift from high to lower concentrations to prevent further serious and acute health consequences [60]. However, most of the established targets (Table II and Table III) have not been met for the last ten years in some locations, which suggests new strategies are needed to reduce the pollution. For instance, approximately 50,000 UK citizens die 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 [61].

The World Health Organization (2016) took measurements of a number of cities – dividing sites into high, middle, and low-income countries within Africa, America, Eastern Mediterranean, Europe, South-East Asia, and the Western Pacific – for air

pollution levels at global and regional level, examining whether they meet or surpass the WHO Air Quality Guidelines annual mean values of 20 µg/m<sup>3</sup> for PM2.5 [58]. According to the latest official report released by WHO (2016), 16% of the assessed population who were globally exposed to more than the PM2.5 annual mean levels. The number of the population exposed to more than the interim target 3 for PM2.5 rises to 27% (IT-3, 30 µg/m<sup>3</sup> for PM10 and 15 µg/m<sup>3</sup> for PM2.5) of the WHO AQG, 46% for IT-2, and 56% for IT-1 [58]. According to the latest air quality database, which covers more than 4000 cities in 108 countries, 97% of cities in low- and middle income countries with more than 100 000 inhabitants do not satisfy the WHO AQG [62]. However, in high-income countries, the percentage declines to 49% [62].

Given that the global trend shows that improvement is required to meet the standards to ensure that air quality has a reduced impact on the causa-

Table II. Annual mean concentrations of PMs and their interim targets [32]

Tabela II. Średnie roczne stężenia pyłu zawieszonego i cele pośrednie

	PM10 (µg/m <sup>3</sup> )	PM2.5 (µg/m <sup>3</sup> )	Basis for the selected level
Interim target – 1	70	35	These levels are associated with about a 15% higher long-term mortality risk relative to the AQG level
Interim target – 2	50	25	In addition to other health benefits, these levels lower the risk of premature mortality by approximately 6% relative to the IT-1 level
Interim target – 3	30	15	In addition to other health benefits, these levels reduce the mortality risk by approximately 6% relative to the IT-2 level
Air quality guideline (AQG)	20	10	These are the lowest levels at which total, cardiopulmonary and lung cancer mortality have been shown to increase with more than 95% confidence in response to long-term exposure to PM2.5

Table III. 24-hour concentrations of PMs and their interim targets (32)

Tabela III. Dobowe stężenia pyłu zawieszonego i cele pośrednie

	PM10 (µg/m <sup>3</sup> )	PM2.5 (µg/m <sup>3</sup> )	Basis for the selected level
Interim target – 1	150	75	Based on published risk coefficients from multi-centre studies and meta-analyses (About 5% increase of short-term mortality over the AQG value)
Interim target – 2	100	50	Based on published risk coefficients from multi-centre studies and meta-analyses (About 2.5% increase of short-term mortality over the AQG value)
Interim target – 3	75	37.5	Based on published risk coefficients from multi-centre studies and meta-analyses (About 1.2% increase in short-term mortality over the AQG value)
Air quality guideline (AQG)	50	25	Based on relationship between 24-hour and annual PM levels

tion of AD, the BRICs were examined as were South American, European, South-East Asian, and East Asian middle-income countries (MICs).

### Brazil, Russia, India and China (BRICs)

The acronym BRIC (Brazil, Russia, India and China) was coined by Jim O'Neill, the English economist, in 2001. At the time of his research, these four developing countries were demonstrating an economic growth rate that was more dramatic than the average rate of other developed countries, such as the U.S.A., Germany, and Japan [63]. It is important to study the BRICs as due to their large populations and notable growth rates and their increasingly influential positions in international politics, the future of the global environment will depend largely on both their policies and as importantly their practices [64]. The recent reports by the United Nations Environment Programme (UNEP) noted that the BRIC countries and the United States have been the main sources of air pollutants, especially in terms of the emission of CO<sub>2</sub>. Hence, 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 prioritize economic goals for ameliorating domestic industries, attracting foreign investment, and educating the workforce in a similar manner to developed countries, over air quality for environmental sustainability, which is linked with the potential development of AD. For example, the World Bank data on the emission of carbon dioxide illustrates that BRIC countries had an increase in the emissions from 2011 to 2015 along with the improvement in their economies: Brazil growing at 1.15%, Russia 12.6%, India 1.7% and China 6.7% [65]. These four countries, comprising a total population of 3 billion people and a GDP of \$16tn, account for greater than one-third of global carbon emissions, not even including the emissions from deforestation and other environmentally damaging land use [66].

As Table 4 shows, a substantial proportion of the population in the BRIC countries are exposed to high levels of PM<sub>2.5</sub> (the level which is more detrimental to human health because of the size capable of entering deeper through the olfactory mucosa), although the numbers are declining slightly in some nations [67].

Table IV. Population exposed to PM<sub>2.5</sub> concentrations exceeding the WHO AQG guideline value in 1998 and 2015 [68]

Tabela IV. Populacje narażone na stężenia pyłu zawieszzonego PM<sub>2,5</sub> przekraczające wartości dopuszczane przez WHO w latach 1998 i 2015

BRIC country	Population (% of total) exposed to PM <sub>2.5</sub> levels above AQG WHO guideline value (10 µg/m <sup>3</sup> ) in 1998	Population (% of total) exposed to PM <sub>2.5</sub> levels above AQG WHO guideline value (10 µg/m <sup>3</sup> ) in 2015
Brazil	99.9	89.5
Russia	90.4	85.7
India	99.9	99.7
China	99.2	99.1

For Brazil, annual average PM<sub>2.5</sub> concentrations in 2015 were about 7–13 µg/m<sup>3</sup> at ten monitoring sites in Rio de Janeiro, 22 µg/m<sup>3</sup> in Sao Paulo, and 7–28 µg/m<sup>3</sup> in six major cities near areas where high traffic volumes are expected [67]. The data illustrates that an estimated 40% of the Brazilian population live with air that contains a greater concentration of PM<sub>2.5</sub> than the WHO annual AQG [67]. The national guideline set for PM<sub>10</sub> concentrations are about 3 times greater than the WHO guidelines; however, the PM concentrations are found to exceed the WHO guidelines by up to 300% [69].

It is estimated that air pollution lead to 49,000 deaths in Brazil every year, with about half of these deaths are accounted for by outdoor pollution, particularly in cities [67]. However, 24,000 deaths result from indoor air pollution, mainly due to cooking with solid fuels and wood, particularly affecting rural communities [70]. Air pollution levels in these households, representing almost 20 million people, are 10–15 times higher than in cities [67]. This value is between 11–26 times greater than 10 µg/m<sup>3</sup> that WHO recommended. The Brazilian government has set interim targets, which aim for 50% adoption of LPG (Liquefied petroleum gas) and improved cook stoves, which are estimated to save 7,350 lives per year [67]. In addition, to find environmental-friendly alternatives, the government has also encouraged the implement of biodiesel as the current projections show that biofuels will account for 30% of the total Brazilian vehicle fuel demand by 2030. This is because the synthesis of the present research claims that diesel-driven automobiles notably contribute to a high percentile of PM in the atmosphere of Brazil, taking up to 34–50% of total PM<sub>2.5</sub> national emissions [71].

Although Brazil does not have the recommended air quality conditions, the atmosphere in the metropolitan areas is cleaner than in other megacities, such as Delhi, Beijing, and Moscow [72], given that the annual PM10 concentration in São Paulo (MASP), Belo Horizonte (MABH), and Rio de Janeiro (MARJ) (the three biggest metropolitan cities in Brazil) are 31, 46.4, and 30.4  $\mu\text{g}/\text{m}^3$ , respectively, and their PM2.5 annual means are 28.1, 17.2, and 14.7  $\mu\text{g}/\text{m}^3$  [72].

In Delhi, the annual mean concentration of PM2.5 in 2000 was between 110 and 170  $\mu\text{g}/\text{m}^3$  [73] – Yet, reached the annual concentration of 286  $\mu\text{g}/\text{m}^3$  in 2010 [74]. In 2014, given that over 40  $\mu\text{g}/\text{m}^3$  is classified as a ‘critical’ level, 8 out of 9 selected areas (Dheerur, Delhi, Pusa, Aya Nagar, Lodhi Rd, Noida, Mathura Road, and Pitamura) in India were exposed to PM10 at a ‘critical’ level, 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 PM2.5 [75]. The Delhi Pollution Control Committee (DPCC) identified that annual average PM2.5 concentration should be cut down by 70% in Delhi to satisfy the annual standard of 40  $\mu\text{g}/\text{m}^3$  as the data from 2014 to 2017 showed that the annual average concentrations were 132  $\mu\text{g}/\text{m}^3$ , 3 times higher than the annual safe standard [10].

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. The population-weighted average PM2.5 concentration reached 59  $\mu\text{g}/\text{m}^3$  in 2010, as in excess of 80% people resided in the region where air quality did not reach the air quality standard (35  $\mu\text{g}/\text{m}^3$ ) in 2010 [74]. The premature mortality caused by PM2.5 has been 1.27 million in China [77,78].

In 2013, 71 cities in China failed to meet the interim WHO target: the cities of Beijing, Tianjin and Hebei were especially advised to lower the PM2.5 levels by 15%, 25%, and 25% respectively by 2017. National levels of PM2.5 were only 4.5% less in 2017 than in 2016, which suggests that pollution increased in southern China. In addition, the costs are high – In 2015 the Clean Air Alliance of China, an advisory group, proposed that the investment cost of the 2013–2018 national plan in Beijing, Tianjin and the surrounding province of Hebei was approximately be 250bn yuan (\$38bn) [79]. Levels of fine-particulate pollution in the Beijing region had fallen by more than 25 percent in 2014 and 2015, as initial cuts bore fruit, but in late 2016 and early 2017 they spiked again [80]. Experts believe

that it would be difficult for Beijing to meet the target of 60  $\mu\text{g}/\text{m}^3$  for the next few years although the average level in 2016 was 73  $\mu\text{g}/\text{m}^3$  (Figure 1) [76].

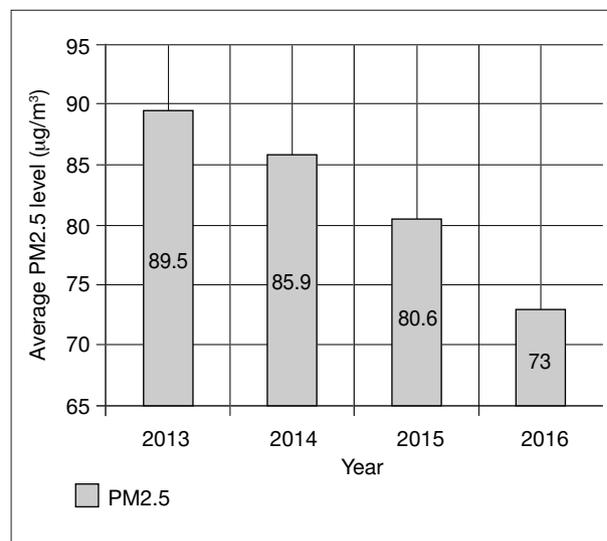


Fig. 1. PM2.5 levels in Beijing between 2013 and 2016, based on Chun [42]

Ryc. 1. Poziomy pyłu zawieszonego PM2,5 w Pekinie w latach 2013–2016 (źródło: Chun)

Although meeting the 2018 target could be difficult, although it may be achieved in the near future as Beijing is now in a better position due to its improved economic structure, which means more direct action can be taken to tackle pollution. China’s Ministry of Environmental Protection (MEP) and Hebei, Tianjin and Beijing governments published air pollution measures to be taken in 2017 [76]. Topics such as the use of coal stoves, popularizing public transport, and closure of unregistered industrial parks of polluting factories outside of the cities have been mentioned [79–83]. The national government announced the closure or cancellation of 103 coal-fired power plants, despite its capacity of generating a total of more than 50 gigawatts of power [80]. The government also said they would cut steel production capacity by another 50 million tons [80]. Emergency shutdowns exact a social expense as well. Elaine Chang, former head of California’s South Coast Air Quality Management District pointed out that the key to success in coping with air pollution is a patient approach that considers the social costs stemming from wages falling and lost industrial jobs, which must be limited as much as possible [81].

On the whole, despite their poor results in meeting the set values of PM10 and PM2.5, there are positive projections, given that these countries have been investing more to the improvement in the en-

vironment along with the increase in their economies. Figure 2 shows the percentage of GDP spent by each of the four countries on development and research to lower the levels of air pollutants. Brazil and China have been attempting to invest their GDP to the development of new alternative energies. India and Russia show the lowest percentages of investment, 0.06 and 0.08%, respectively – However, they still show an increase in their investments [84].

	Brazil	Russia	India	China
2000	1.02	1.05	0.74	0.90
2001	1.04	1.18	0.72	0.95
2002	0.98	1.25	0.71	1.07
2003	0.96	1.29	0.71	1.13
2004	0.90	1.15	0.74	1.23
2005	0.97	1.07	0.81	1.32
2006	1.01	1.08	0.80	1.39
2007	1.10	1.12	0.79	1.40
2008	1.11	1.04	0.84	1.47
2009	1.17	1.25	0.82	1.70
2010	1.16	1.13	0.80	1.76

Fig. 2. Percentage of GDP invested to research and development from 2000 to 2010 (Source: [65] modified)

Ryc. 2. Procent PKB przeznaczony na inwestycje w badania i rozwój w latach 2000–2010 (źródło [65], modyfikacja własna)

## European Union (EU)

The EU limit values 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 (Table V).

Table V. 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 [48]

Tabela V. Wartości maksymalne i cele pośrednie dla pyłu zawieszonego PM10 i PM2,5 wg Dyrektywy w sprawie jakości powietrza w UE i wytycznych WHO dotyczących jakości powietrza

Size Fraction	Averaging period	EU Air Quality Directive (Objective and legal nature and concentration)	WHO guidelines
PM10	1 day	Limit value: 50 $\mu\text{g}/\text{m}^3$	50 $\mu\text{g}/\text{m}^3$
PM10	Calendar year	Limit value: 40 $\mu\text{g}/\text{m}^3$	20 $\mu\text{g}/\text{m}^3$
PM2.5	1 day	25 $\mu\text{g}/\text{m}^3$	25 $\mu\text{g}/\text{m}^3$
PM2.5	Calendar year	25 $\mu\text{g}/\text{m}^3$	10 $\mu\text{g}/\text{m}^3$

In 2015, approximately 19% of the EU-28 urban population was exposed to PM10 above the EU daily limit value. The percentage of exposure above this EU daily limit value fluctuated between 16 % and 43 % over 2000–2015. Additionally, 53 % of the equivalent urban population was exposed to concentrations beyond the stricter WHO AQG value for PM10 in 2015. The percentage of the urban population exposed to levels exceeding the WHO annual AQG (20  $\mu\text{g}/\text{m}^3$ ) ranged from 50% to 92 % in 2000–2015 [86].

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 shows that countries recognized as high income countries (HIC), located in the west of Europe, have generally lower concentrations of PM2.5, while countries with lower Gross Domestic Product (GDP) in the east have higher concentrations [86]. This establishes a relationship between economic activities and the PM concentrations, which suggests that it would be difficult to enforce PM guideline values, as it is difficult for some lower income countries (LICs) to limit their activities producing PM as they focus on economic growth. 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.

## London

Drilling down from cases of BRICs and the EU, London is a particularly significant area of investigation. With the rapid urbanization coincided with increasing population, London has been recognized as one of the busiest cities in the world. Such urbanization has exposed people to pollution from heavy traffic flow as well as other sources of PM (Figure 4). Mounting rates of AD are linked with the traffic situation in London, given that AD risk lessened as people resided farther away from traffic roads. 7% of AD risk increased by living within 50 metres, 4% at 50–100 metres and 2% at 101–200 meters [88]. It should be noted that house prices generally decline closer to main roads, which explains that a socially defined exposure Traffic emissions account globally for 25% of ambient PM2.5 [89]. London's annual PM10 and PM 2.5 concentration reached 22  $\mu\text{g}/\text{m}^3$  and 16  $\mu\text{g}/\text{m}^3$  in 2011 [73]; this abridged value can be owing to the congestion

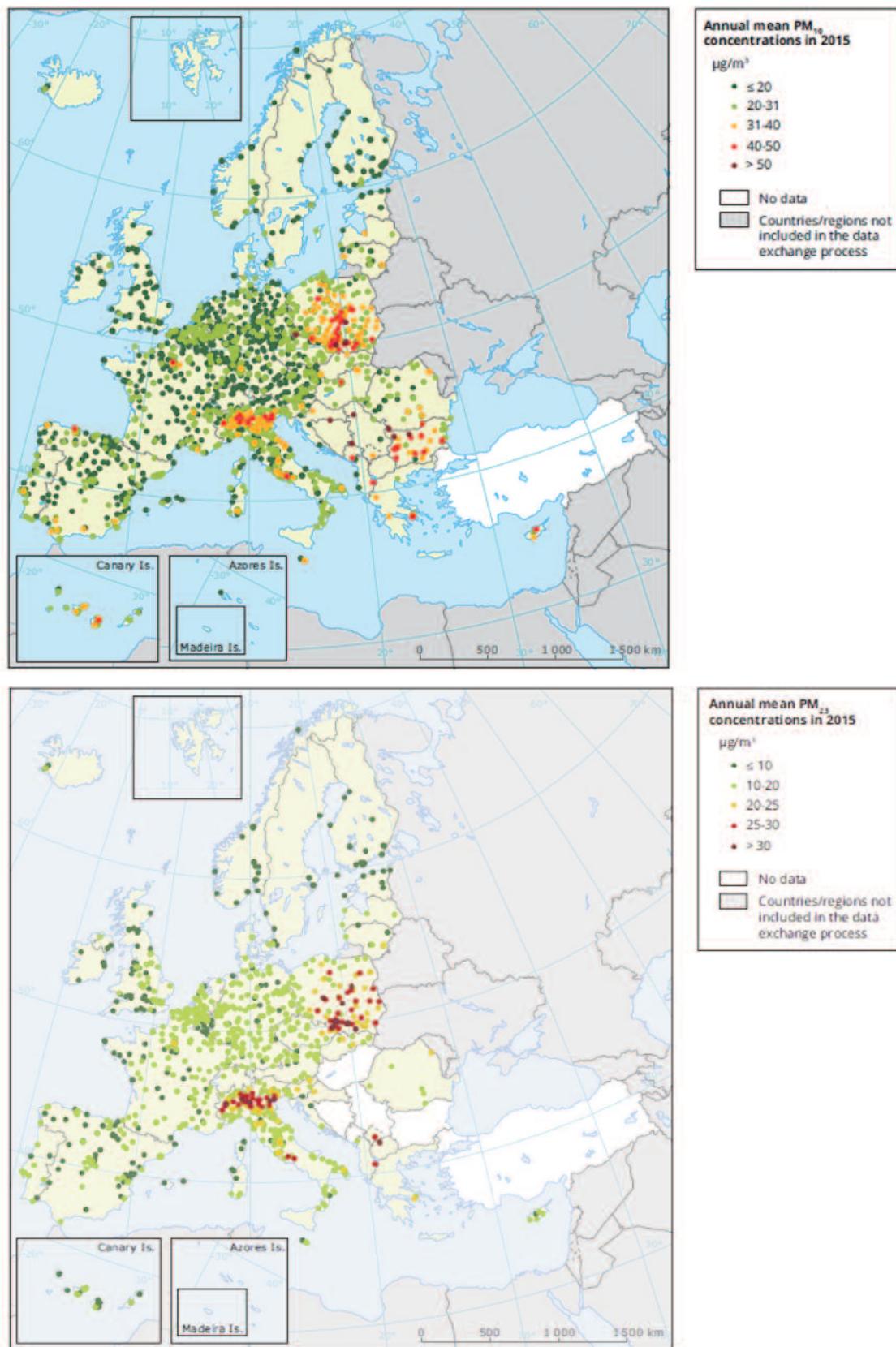


Fig. 3. PM<sub>10</sub> and PM<sub>2.5</sub> annual mean concentrations in 2015 [87].

Ryc. 3. Średnie roczne stężenia pyłu zawieszonego PM<sub>10</sub> i PM<sub>2.5</sub> w roku 2015

charging schemes as well as the emissions and traffic interventions [89]. Nevertheless, London still surpasses the set values based on the WHO limits for PM<sub>2.5</sub> and PM<sub>10</sub>: 2 µg/m<sup>3</sup> in exceedance for PM<sub>10</sub> and 6 µg/m<sup>3</sup> in exceedance for PM<sub>2.5</sub> in 2018. [89].

The estimated economic expenses on the health care system in London of air pollution have been calculated at between £1.4 billion per year, which

only reflects PM [91].

However, it is controversial whether Brexit will trigger confusion and uncertainty over air quality policy, and whether a new Clean Air Act will ensure UK residents' legal protections following the UK leaving the European Union. As aforementioned, most of the air quality policies in the UK are based on the EU directives.

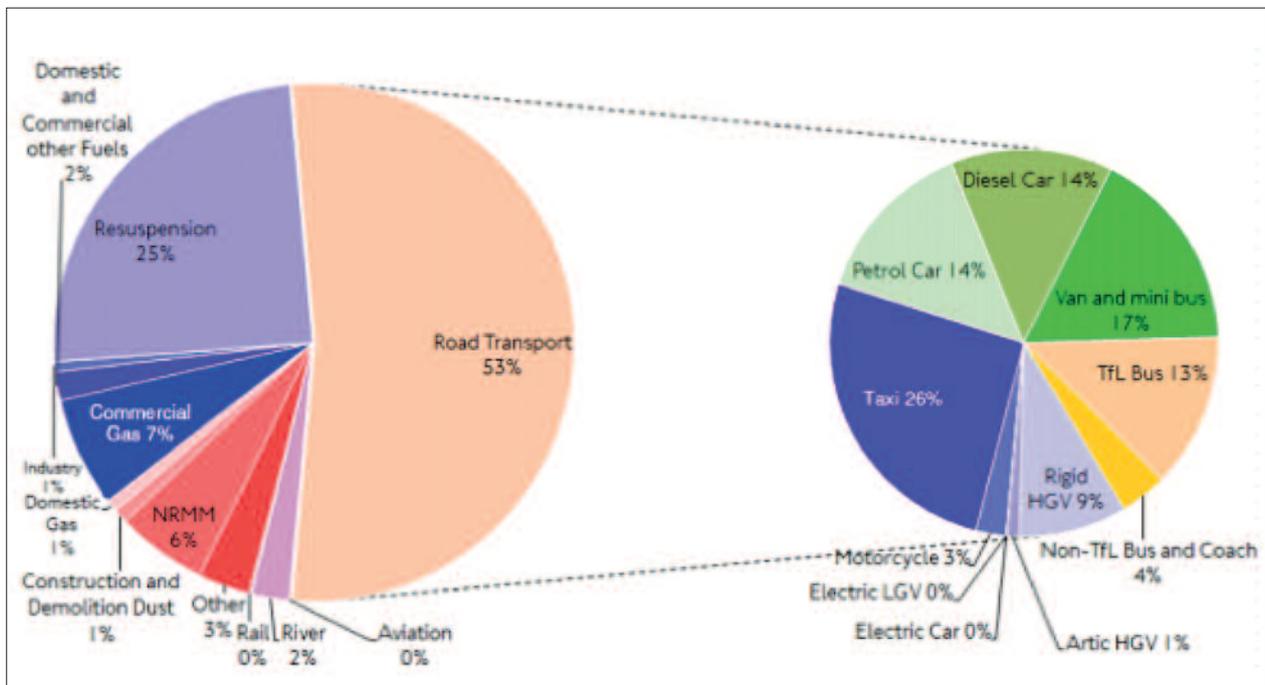


Fig. 4. Sources of PM in London [Source from Laei, 2016 [90]]

Ryc. 4. Źródła emisji pyłu zawieszonego w Londynie

### WOULD PREVENTION OF AIR POLLUTION BE A BETTER SOLUTION TO ALZHEIMER'S DISEASE THAN DEVELOPING MEDICATION?

It has been shown that PM<sub>2.5</sub> exposures can result in AD due to the neuro-inflammatory responses, and the increased likelihood of developing AD due to PM<sub>2.5</sub> can be greater among the relatively less socio-economically developed communities, who are more likely to be exposed to contaminated 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 [92]. Perhaps, such low emphasis is driven in part by a focus that prioritises economic development over health impacts, particularly in LICs.

Here, we 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) moral hazard is a point to be mentioned for less socio-economically developed communities.

The conclusion of this discussion points towards the development of AD cures being a more suited approach, despite approaching the problem through simultaneous measures being necessary.

### ***(1) Combatting air pollution is more likely to draw political attention***

Prior to 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 N-Methyl-D-aspartate (NMDA) receptor antagonists, which restore lowered levels of acetylcholine. This helps to convey information between certain nerve cells and inhibit the hypofunction of NMDA receptor that can cause memory deficits [93]. 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 [94]. 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 [94].

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 £90 million [95], and while the US government spends \$200 billion on AD care, it spends less than 1% of that sum on research [96]. This could explain the slow development of medications, despite AD continuing to be the World's 6<sup>th</sup> leading cause of death [96].

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 0.7 billion £ out of the 46.2 billion£ public sector gross investment [97]. The health sector's estimate was £4.6 billion, but the specific allocation provided was heavily concentrated on National Health Service NHS insurance, rather than research investment [97]. 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 prob-

lem 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 relationship to PM made explicit.

### ***(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 [95]. 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 PMs 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, because the previously mentioned investment is currently lacking.

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 PMs 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 [98]. Moreover, China's economic progress is firmly powered by cheap coal, which is the main source of PM<sub>2.5</sub> concentration level. Coal combustion contributes 40% to the total national level and up to 50% in Sichuan Basin [98]. 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 [99]. Further investment in tackling air pollution would reduce health-care costs as a decrease in PM<sub>2.5</sub> 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) \$2 trillion can be saved by 2020 through the prevention of further deaths and illnesses caused by air pollution [97]. 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.

### (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<sub>2.5</sub> 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 [97]. 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<sub>2.5</sub>, as argued by Becker (2013) that “*environmental protection as a priority stems from affluence*” [14]. 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 [97].

This is especially true since there are still many ways in which HICs can contribute to the problem of PMs 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<sub>2.5</sub> 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 PMs [100].

Secondly, fabric filters (FF) and electrostatic precipitators (ESP) are the two most widely applied conventional particulate emission control devices. ESPs can collect 98% of PM<sub>2.5</sub> 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<sub>2.5</sub> [101].

It is evident that such measures can positively impact the health of the citizens of the respective countries - and this is why HICs had to force LICs to act even more ironic. This is because HICs themselves are 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<sub>2.5</sub> exposure to 15 µg/m<sup>3</sup>, 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<sub>2.5</sub> reached approximately 23 µg/m<sup>3</sup> in 2000 [102]. Even though it has been reduced to 17.67 µg/m<sup>3</sup> in 2016, it is still higher than the WHO's recommended level [58,102]. 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.

For this reason, eco-tax should be enacted by the UN as an efficient way of reducing air pollution and lowering the risk of the development of AD. Eco-tax is a tax levied on activities regarded to be environmentally harmful and it attempts to promote environmentally-friendly activities via economic incentives [98]. This applies when the activity is based on a production process, consumption, or disposal of waste. Both the consumer and producer

will bear the costs of their input factors, confirming the consumption and production to be economically justifiable [98]. Through eco-tax, consumers and businesses will attempt to determine the most cost-effective way of reducing the environmental damage with flexibility. Eco-tax raised in HICs can support LICs' economic activities with the environmental-friendly technology they currently have, or financial aid could be given to LICs. This can possibly lessen the negative effect of eco-tax, which would otherwise hit the poorest, most polluting countries who cannot afford the new expensive technology. It should be made clear that, however, due to the nature of the policy being taxation, this process should be gradual than immediate. In order to minimize the effects to the firms and the people, the tax rate should gradually reach the ideal point, rather than be enforced immediately.

## 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 risk factors of developing AD through increasing the expression of COX2 and Amyloid-beta. 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 combatting 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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