Journal of Health and Social Sciences Advance Publication Online
Published Online October 4, 2018 doi10.19204/2018/twrd2

ORIGINAL ARTICLE IN EVIRONMENTAL PUBLIC HEALTH

Toward a new interdisciplinary model to understand Alzheimer's disease: The interplay between neurobiology and socio-economic factors

Hyun Jee Han[1], Clive Shrubsole[2]

Affiliations:

[1] Pharmaceutics, School of Pharmacy, University College London, London, UK

[2] Honorary Senior Research Associate, The Bartlett School of Environment, Energy and Resources, University College London, London, UK

Corresponding Author:

Hyun Jee Han, Pharmaceutics, School of Pharmacy, University College London, 29-39 Brunswick Square, London, UK, WC1N 1AX. E-mail: sarah96120@gmail.com.

Abstract

Introduction: In recent years, there has been emerging evidence that air pollution is a chronic source of neuroinflammation, which contributes to Alzheimer's Disease (AD) and other forms of dementia, which are an increasingly common and devastating illness affecting elderly populations. Aim of this paper is to develop a new, interdisciplinary and theoretical model based on neurobiology, sociology of medicine and eco-political science for a better understanding of the etiopathogenesis of Alzheimer's disease and other forms of dementia.

Methods: We carried out a literature review focusing on the following aspects: 1) The causal relationship between $PM_{2.5}$ (and air pollution) and AD; 2) Regulations and guidelines about air pollution released by organizations across the world; 3) Differences in $PM_{2.5}$ and educational

levels between More Economically Developed Countries (MEDC) and Less Economically Developed Countries (LEDC); 4) Differences of AD incidence between MEDC and LEDC with regard to their levels of social developments.

Results: Our interdisciplinary model depicts a pathway through which specific socio-economic factors (poor residential conditions and geographical sites, low educational levels) and environmental factors (i.e. air pollution exposure) interact to increase the risk of developing Alzheimer's disease.

Discussion: According to our model, socio-economically disadvantaged individuals and communities are likely to be at higher risk for AD, 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 low educational levels. This suggests that the lower the socio-economic development, the higher the chance of being exposed to the $PM_{2.5.}$ These combined socio-economic determinants may result in a greater likelihood of developing AD.

Conclusion: Although our model does not include other well-recognized causes of AD and needs to be tested by further in-depth epidemiological studies, more holistic and realistic views on the current approaches will allow this field to move forward and lead to an improvement to actionable policies.

KEY-WORDS: Neuroinflammation; Alzheimer's disease; air pollution; $PM_{2.5}$; eco-politics; education; Models, theoretical; socioeconomic factors.

Journal of Health and Social Sciences Advance Publication Online
Published Online October 4, 2018 doi10.19204/2018/twrd2

Riassunto

Introduzione: In anni recenti, è emersa l'evidenza che l'inquinamento atmosferico sia una sorgente cronica di neuroinfiammazione, che contribuisce al Morbo di Alzheimer ed altre forme di demenza che rappresentano un tipo di malattia sempre più comune e devastante che interessa la popolazione anziana. L'obiettivo di questo studio è quello di sviluppare un nuovo modello teorico interdisciplinare basato sulla neurobiologia, la sociologia della medicina e la scienza eco-politica per una migliore comprensione dell'etiopatogenesi del Morbo di Alzheimer e di altre forme di demenza.

Metodi: Abbiamo effettuato una revisione di letteratura focalizzata sui seguenti aspetti: 1) la relazione causale tra il $PM_{2.5}$ e l'inquinamento atmosferico ed il morbo di Alzheimer; 2) i regolamenti e le linee guida sull'inquinamento atmosferico emanate dalle organizzazioni in tutto il mondo; 3) le differenze nei livelli di $PM_{2.5}$ ed educativi tra i Paesi economicamente più sviluppati ed i Paesi economicamente meno sviluppati; 4) le differenze nell'incidenza del Morbo di Alzheimer tra i Paesi economicamente più sviluppati ed i Paesi economicamente meno sviluppati con riguardo ai loro livelli di sviluppo sociale.

Risultati: Il nostro modello interdisciplinare definisce una via attraverso cui specifici fattori socio-economici (località geografiche e condizioni abitative indigenti, bassi livelli di educazione) ed ambientali (ovvero esposizione all'inquinamento atmosferico) interagiscono per incrementare il rischio di sviluppare il Morbo di Alzheimer**.**

Discussione: Secondo il nostro modello, gli individui e le comunità economicamente svantaggiate sono probabilmente a più alto rischio di sviluppare il Morbo di Alzheimer rispetto a quelli che vivono in condizioni di vita migliori, per una maggiore probabilità di vivere in aree abitative a

basso valore e con maggiore esposizione ad inquinamento atmosferico e per i bassi livelli educativi. Questo suggerisce che minore è lo sviluppo socio-economico, maggiore è la probabilità di essere esposti a $PM_{2.5.}$ Questi determinanti socio-economici in combinazione possono determinare una maggiore probabilità di sviluppare il Morbo di Alzheimer.

Conclusione: Sebbene il nostro modello non includa altre ben riconosciute cause di Morbo di Alzheimer e necessiti di essere testato in ulteriori approfonditi studi epidemiologici, una maggiore visione olistica e concreta sugli approcci attuali consentirà a questo settore di fare progressi e di portare ad un miglioramento delle politiche attuabili.

TAKE-HOME MESSAGE: In this paper, we have developed a new interdisciplinary theoretical model based on neurobiology, sociology of medicine and eco-political science to understand Alzheimer's disease and other forms of dementia, to move forward and lead to an improvement to actionable policies.

Competing interests: none declared

Cite this article as: Han HJ, Shrubsole C. Toward a new interdisciplinary model to understand Alzheimer's disease: The interplay between neurobiology and socio-economic factors. [published online ahead of print October 4, 2018]. J Health Soc Sci. doi10.19204/2018/twrd2.

DOI 10.19204/2018/twrd2

Received: 18 Aug 2018 **Accepted:** 20 Sep 2018 **Published Online:** 04 Oct 2018

INTRODUCTION

Health disparities across life spans have been observed among the individuals from different milieus and specific geographical areas based on their socio-economic circumstances [1]. Living in certain geographical areas and with provided conditions can influence a broad range of biological and environmental processes that in turn affect health [2]. For instance, the degree to which one can be exposed to airborne pollution shows a correlation with social disadvantage in the United States, due to declines in land and property values near highways and industrial areas, where some airborne pollution originates [3]. The number of patients suffering from air pollution is correlated with their standard of living, such as the level of education available. Therefore, it is it is conceivable that poorer communities with more socio-economically disadvantaged individuals tend to be exposed to higher levels of airborne pollution [1]. 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%) [4] – especially particulate matter (PM) – which has been the 5th highest ranking health risk factor [5]. Out of the numerous health impacts, the link between PM and Alzheimer's disease (AD) has gained a lot of attention, which can affect over 13 million people worldwide at a cost of more than $ 600 billion [6, 7]. Alzheimer's disease (AD) is the most common type of dementia, accounting for about 60-80% of cases [8] Annual incidence is estimated at 0.6% for older persons aged 65-69, but for those above 85, the incidence increases to 8.4% [9]. 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 [10-12]. Since air pollution is one of the most prevalent sources of oxidative stress and neuro-inflammation, which we confront on

a daily basis, it is a very important environmental risk factor to consider for AD [13]. The vast majority of previous studies on the causes of AD focus on other factors such as ageing, genetics (family history of AD, the presence of APOE-4 alleles, being a member of the female sex), cardiovascular disease, head injury, Down syndrome and low educational level [7]. However, it is now the time to explore the new hypothesis, long-term $PM_{2.5}$ can trigger and exacerbate AD worldwide, which has not been investigated for a long time due to scarce data available on the linkages between $PM_{2.5}$ and AD [6]. Individuals with low social and economic status tend to be already in communities where poor facilities are provided to support health (e.g. poor public health education and low numbers of health care services). These communities tend to focus on economic activities rather than improving the environment, which can potentially cause more potent inflammatory responses and result in increased risk of AD, due to the exposure to various harmful physical and social factors [14]. It was reported that a Taiwan cohort of 95,690 individuals from the age of 65 demonstrated a strong relationship between long-term exposures to $PM_{2.5}$ above the current US Environmental Protection Agency (EPA) standards and increased risk of AD [15]. This paper has a double aim. Firstly, to review and integrate research from several disparate, but relevant fields –neuroscience, psychoneuroimmunology, environmental toxicology, and political and social science – in order to suggest an interdisciplinary model to understand how more disadvantaged socio-economic conditions at individual and community levels may increase vulnerability to the development of AD and other forms of dementia. Secondly, we propose strategies to reduce air pollution within a more holistic approach to policy decision-making, which can support sustainable economic activities.

Journal of Health and Social Sciences Advance Publication Online
Published Online October 4, 2018 doi10.19204/2018/twrd2

METHODS

The Study Framework

This paper clarifies how the World Health Organisation (WHO) regards air pollution, and the extent to which each government attempts to react towards the phenomenon by following the current political and socio-economic policies that try to cut such pollutants. Especially, BRIC countries (Brazil, Russia, India, and China), the EU, USA and UK will be investigated additionally from the case of the WHO, prior to drilling down into New York and London (Figure 1). New York and London are interesting case studies due to the various economic activities, where people's understanding and attention towards environmental issues co-exist. Countries for study were selected based on their socio-economic status, given that "environmental protection as a priority stems from affluence" [16].

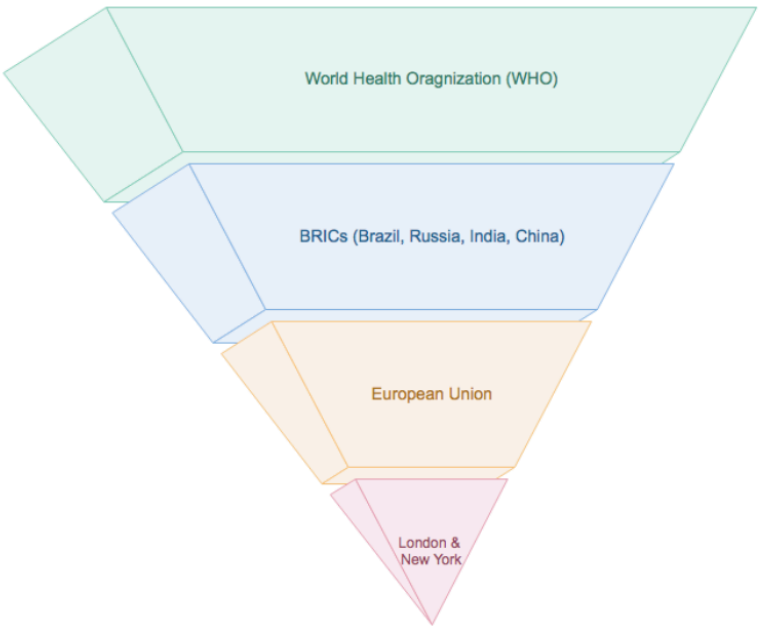


Figure 1. An inverted pyramid graph showing a top down approach of different regulatory government bodies for air pollution, illustrating the ways in which case studies are arranged in this study.

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 pollutants have to be both detailed and accurate enough to influence research data [17]. 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 [18]. Thus, this paper often refers to the *in vitro* and *in vivo* studies carried out by Block & Calderón-Garcidueñas (2009), in order to establish certitude of 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 realization that more sources for evidence are required. The assessment of cumulative and the corresponding reactions require 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. In addition, in order to establish a correlation between the level of $PM_{2.5}$ or prevalence of AD in a particular area and socio-economic levels, the Human Development Index (HDI) has been used throughout the research to refer to the education level and GNI per capita. This is due to their nature as a composite index, providing a useful overall socio-economic performance of a country. For example, the level of education is measured based on both adult literacy rate and years of schooling.

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 and then expanded as the research progressed.

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.

RESULTS AND DISCUSSION

Atmospheric air pollution and $PM_{2.5}$

Atmospheric air pollution is defined as ‘any chemical, physical, and biological pollutant found in the air outdoor or indoor, which can potentially chance the natural features of the

atmosphere' [19], as well as any matter which pollutes the atmosphere without getting absorbed through natural environmental flows and cycles, due to its nature and quantity [20]. The World Health Organization has claimed that the biggest environmental factor harming the human health is air pollution [4]. Outdoor (ambient) air pollution is a mixture of gaseous and particulate components, including carbon monoxide (CO), lead, ozone, nitric oxide (NO_2), sulphur dioxide (SO_2), and particulate matter (PM), which can all potentially affect health in a negative way [21].

PM is the prominent airborne pollutant, which is attributable to the various health threats. PM has a range of sizes, from wind-blown dust particles (< 10 μm) to ultrafine particles (> 100 nm), where the small size accounts for their impact in biological processes as they can cross into the blood stream from the lungs [22]. PM particle components consist of toxic elements on the surface, including polyaromatic hydrocarbons, which vary according to the season, geographical location, and the source of the PM. The high number of compounds absorbed on PM are considered neurotoxic [23,24]. Particles larger than 10 μm in diameter are 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 2.5 μm aerodynamic diameter ($PM_{2.5}$), and ultrafine (UFPs/ UFPM) or nano-particles (NP) of less than or equal to 0.1 μm [25,26]. 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 [25]. 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 [25]. In addition, both organic and inorganic compounds, such as sulphates, nitrates, carbon, lipopolysaccharide, ammonium, metals, hydrogen ions and water form $PM_{2.5}$ [13]. It is important to note that diesel

exhaust particles (DEPs) are a main source among the ambient fine particles in urban environments [27]. The smaller fractions of PM (< 2.5 μm) can result in lung deposition and the penetration of the respiration tract, overall gaining access to the blood stream and nervous system [28]. 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 [29]. $PM_{2.5}$ 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 [30]. In addition, they are exposed to worse air quality throughout their lifespan [21], 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 that can help protect susceptible populations and in turn reduce health disparities, and the likelihood of AD.

Inflammatory mechanisms induced by the link between Alzheimer's Disease and air pollution

Once the large surface-to-volume ratio of small $PM_{2.5}$ is taken into the body, it can readily enter not only the cell membranes and the barriers in the lung and the brain, but also erythrocytes and neurons [31], via several routes (Figure 2). For example, the inhaled PMs can enter the lungs through penetrating the alveolar-capillary barrier, depending on their size, charge, chemical compositions, and likelihood of producing aggregates [32]. One of the ways through which PMs enter the nervous system is the olfactory mucosa [33]. $PM_{2.5}$ can pass through the olfactory

receptor neurons (also known as bipolar sensory neurons) or trigeminal nerve, which help them, reach the brain by pinocytosis, receptor-mediated endocytosis and simple diffusion [34]. Olfactory sensory neurons can expand their dendrites through the mucous layer, which covers the olfactory epithelium and interacts with odorants in the air directly, despite the olfactory epithelium, which is covered by a layer of sustentacular cells. As they merge into sensory neurons, they are transported to the olfactory bulb along the axons through slow axonal transport [35]. From this point, the PM particles can be carried into the various brain regions, including the amygdale, hypothalamus, piriform cortex, olfactory cortex, and anterior olfactory nucleus [34]. Uptake through the nasal route can be deeper because of the additional pollutant-induced systemic inflammation, which reduces the olfactory mucosal barrier, causing an enhanced neuropathology [34]. The CNS can be activated by ground-level ozone exposure via the vagal nerves even without interaction with the thoracic spinal nerves [36].

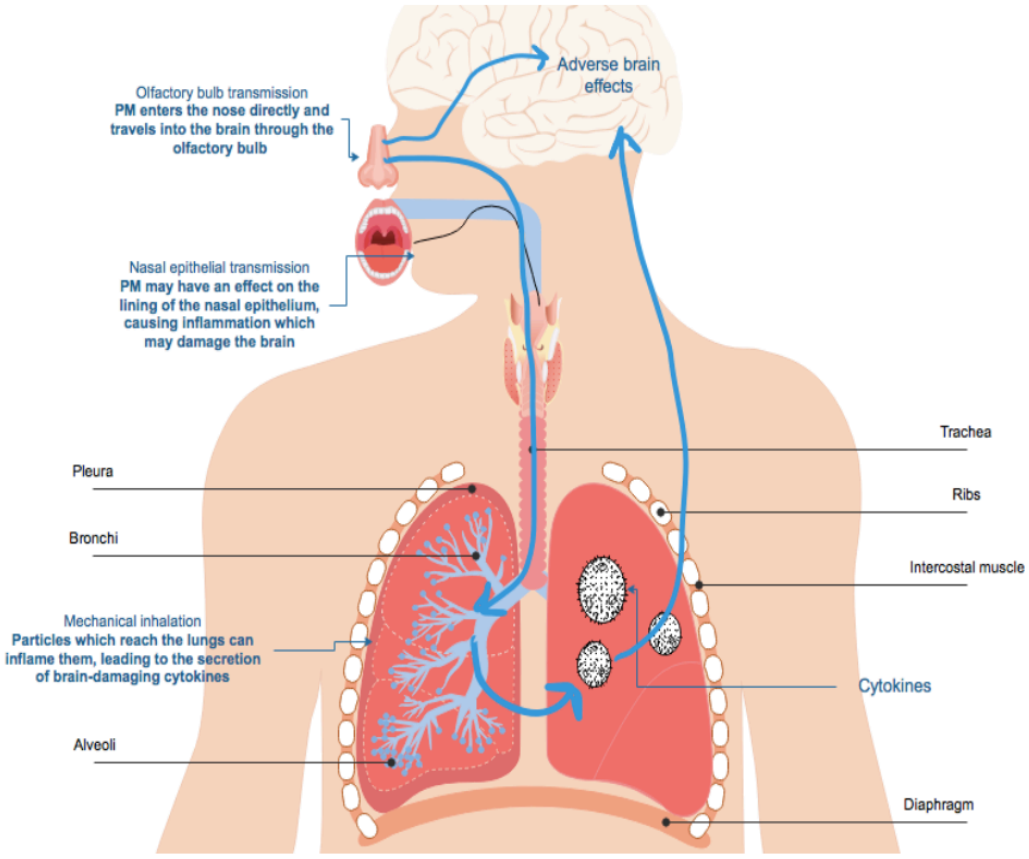


Figure 2. The possible pathways for air borne pollutants to enter the brain.

Alzheimer's disease pathogenesis is associated not only with the neuronal compartment, but also with the interactions between immunological mechanisms in the brain. Innate immune responses can be triggered when misfolded and aggregated proteins bind to microglia and astroglia through pattern recognition receptors. According to genome-wide analysis, there are genes, which encode factors for regulating glial clearance of those misfolded proteins and inflammatory reaction. External factors, including systemic inflammation, can exacerbate the disease progression through interfering with immunological processes of the brain.

Block and Calderón-Garcidueñas (2009) confirmed the association of air pollution with neuroinflammation and AD through experimental studies with interesting results. They have

demonstrated that “Feral dogs living in regions of high pollution showed enhanced oxidative damage, premature presence of diffuse amyloid plaques, and a significant increase in DNA damage (apurinic/apyimidinic sites) in olfactory bulbs, frontal, cortex, and hippocampus” [13]. Thus, we can question the mechanism behind the triggering of inflammation by the toxic pollutants in the air, and in turn, the immune cells involved in the elimination of the toxic substance in human bodies. Systemic inflammation can be associated with various clinical implications, such as memory impairment, sickness behaviours, and seizures [37]. Production of pro-inflammatory cytokines including tumour necrosis factor alpha (TNFα), interleukin-1 beta (IL-1β), and interleukin-6 (IL-6) results in systemic inflammation, which causes the blood vessels in the brain to expose a constitutive expression of receptors [38]. Specifically, mice tend to recruit a bigger number of circulating monocytes to the brain in response to the injection of TNFα. The elevated plasma cytokine interleukin-6 concentrations affect the circulation because of interactions between airway epithelial cells, alveolar macrophages, and particles. The cytokines can then activate the cerebral endothelial cells, interrupting the blood-brain barrier (BBB) integrity or stimulating the signalling cascades, which can result in the activation of nuclear factor kappa B transcription factor-mediated pathways and mitogen-activated protein (MAP) kinase. Circulating cytokines produced in systemic inflammation lead to neuroinflammation, neurotoxicity, as well as cerebral vascular damage. For example, one large pro-inflammatory insult with a single IP injection of high concentrations of LPS and TNFα in adult animals causes chronic neuroinflammation, which continues even after peripheral inflammation falls. This indicates delayed and progressive neuron death [39]. The entire process in mice begins only after 7-10 months after the LPS treatment. Disruption of the BBB, owing to PM, leads to trafficking of inflammatory cells and mast cells exhibiting surface proteins CD163, CD68, and HLA-DR to the damaged site [33]. Moreover, inflamed peripheral organs or endothelial cells release cytokines,

which enter the brain via diffusion or active transport, exacerbate the conditions in a synergic way by activating peripheral neuronal afferents, and stimulate the peripheral innate immune cells. When compared to 'leaky' vessels located peripherally, cerebral micro-vessels are a tough barrier to various toxins, small organic drugs, and macromolecules [40]. Therefore, these small vessels within the brain parenchyma form the blood-brain barrier (BBB) which functions as a physical and chemical barrier of metabolizing enzymes, transporter proteins and other various cell types PM can interact with cells comprising the BBB and navigate across it [41]. For example, aluminium nanoparticles diminish our brain microvascular endothelial cell viability, affecting mitochondrial potential, oxidative stress and protein expression, which all damage the BBB [42]. For those residing in heavily polluted areas, the PM-induced up-regulation of efflux transporters (P-glycoprotein and Multidrug Resistance Associated Protein-2) at the BBB can have implications for drug availability in the brain parenchyma. In addition, PM can mobilise bone-marrow-derived monocytes and neutrophils into the circulating bloodstream in both human and animal studies [32]. Together with neuronal damages, it is also suggested that systemic inflammation driven by air pollution can lead to deteriorating respiratory, olfactory, and blood-brain barriers to augment access to the CNS and increase neuropathology further [43]. Given these findings, it is not surprising to see that air pollution is linked with neuroinflammation, which contributes to AD. Figure 3, based on Genc et al. (2011)'s proposal, visually demonstrates how air pollution can result in AD and Neuronal death at the end.

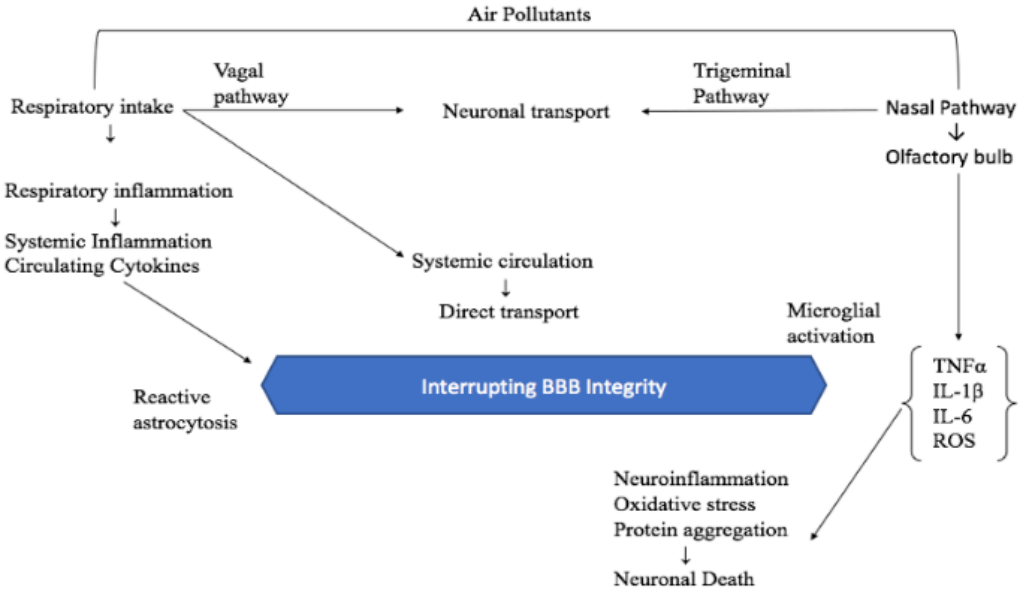


Figure 3. The impact of air pollution on the brain via multiple mechanisms. (Source: Genc et al. modified [34]).

Table 1. Main studies about correlation between air pollution, neuroinflammation and Alzheimer's disease.

Author and year	Findings
Mills, et al, 2009 [32]	Inhaled $PM_{2.5}$ or NP (Nano-sized particles) are small enough to penetrate the alveolar-capillary barrier, according to their size, charge, chemical compositions, and risk of producing aggregates.
Lewis, et al, 2005 [44]	PMs can enter the nervous system directly through the olfactory mucosa.
Genc, et al, 2012 [34]	PMs can be carried into various brain regions through pinocytosis, receptor-mediated endocytosis and simple diffusion. Uptake through the nasal route can be greater because of the extra pollutant-induced systemic inflammation, which lowers the olfactory mucosal barrier, causing an enhanced neuropathology.
Calderón-Garcidueñas, et al, 2002 [43]	Together with neuronal damages, it is also claimed that systemic inflammation driven by air pollution can lead to deteriorating respiratory, olfactory, and blood-brain barriers to augment access to the CNS and increase neuropathology further.
Calderón-Garciduenãs, et al, 2008 [33]	Disruption of the BBB, owing to PM, leads to trafficking of inflammatory cells and mast cells exhibiting surface proteins CD163, CD68, and HLA-DR to the damaged site. PM can interact with cells comprising the BBB and navigate across it.

Block and Calderón-Garcidueñas, 2009 [13]	Interesting experimental results showed an association between air pollution and neuroinflammation. Feral dogs from highly polluted areas demonstrated greater oxidative damage, premature presence of diffuse amyloid plaques, and a significant increase in DNA damage in hippocampus, cortex, frontal, and olfactory bulbs.
Teeling & Perry, 2009 [38]	Constitutive expression of receptors can be shown due to the production of pro-inflammatory cytokines which result in systemic inflammation.
Qin, et al, 2007 [39]	One large pro-inflammatory insult with a single IP injection of high concentrations of LPS and TNFα in adult animals causes chronic neuroinflammation, which continues even after peripheral inflammation falls. This indicates delayed and progressive neuron death.

Regulations about air pollution across the world

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.

World Health Organisation

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 (AQG) were produced to suggest a guidance in alleviating the health impacts of air pollution, based on current scientific evidence [4]. The World Health Organization (2006) has promoted 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 guidelines specify targets for a wide range of policy options for air quality management that should be considered by policy-makers [45]. They are based on four common air pollutants: Ozone (O_3), sulphur dioxide (SO_2), nitrogen dioxide (NO_2), and particulate matter (PM) [4].

Together with guideline values, interim targets have been set for each pollutant to let a progressive decline in air pollution in highly polluted sites. The targets confirm a shift from high concentrations to lower concentrations of air pollutant to prevent further severe and acute health consequences [45]. However, a majority of the established targets (Table 1 and Table 2) have not been met for the last ten years, which implies new strategies are needed to reduce the pollution.

Table 2. WHO air quality guidelines and interim targets for particulate matter: annual mean concentrations (Source: World Health Organization, 2016).

	$PM_{2.5}$ ($\mu g/m^3$)	**Basis for the selected level**
Interim target -1	75	According to published risk coefficients from multi-centre studies and meta-analyses (Estimated 5% rise of short-term mortality over the AQG value).
Interim target – 2	50	On the basis of published risk coefficients from multi-centre studies and meta-analyses (Estimated 2.5% rise of short-term mortality over the AQG value).
Interim target – 3	37.5	On the basis of published risk coefficients from multi-centre studies and meta-analyses (Estimated 1.2% rise in short-term mortality over the AQG value).
Air Quality Guideline (AQG)	25	In the light of the association between 24-hour and annual PM levels.

Table 3. WHO air quality guidelines and interim targets for particulate matter: 24-hour concentrations for management purposes (Source: World Health Organization, 2016).

	$PM_{2.5}$ ($\mu g/m^3$)	**Basis for the selected level**
Interim target -1 (IT-1)	35	These levels are related to a 15% higher long-term mortality risk relative to the AQG level
Interim target – 2 (IT-2)	25	Along with other health benefits, these levels decrease the risk of premature mortality by roughly 6% relative to the IT-1 level
Interim target – 3 (IT-3)	15	In addition to other health benefits, these levels lower the mortality risk by approximately 6% relative to the IT-2 level
Air Quality Guideline (AQG)	10	These are the lowest levels at which total, cardiopulmonary and lung cancer mortality have been demonstrated to rise with more than 95% confidence with regards to long-term exposure to $PM_{2.5}$.

BRICs (Brazil-Russia-India-China)

With the currently large populations in Brail, Russia, India, and China (the BRICs), they are in increasingly influential positions in international politics with notable socio-economic growth rates. The BRICs are a significant case to analyse, as there is a possible correlation between the risk of developing AD and socio-economic development as economic goals are often prioritised over environmental air quality in less socio-economically developed countries despite its link with the potential development of AD. There have been many reports asserting that the future of the global environment will depend hugely on policies and practices of the BRICs [46]. In 2008, over one-third of global carbon emissions were attributable to the BRICs, not even counting the emissions from deforestation and other environmentally inadequate land use [47]. Since the BRICs comprise both developing and developed aspects, they are left in a bind when trying to balance the requirements of their populations with environmental sustainability. Similar to High Income

Countries (HICs), for example Western Europe and the U.S., their priorities are to improve standard of living as well as quality of life, including improvements in domestic industries, education of the workforce, and attracting a high foreign investment [47]. The BRICs also aim to follow the WHO guideline values, which are very doubtable in terms of whether they will be able to meet the guidelines or not.

European Union (EU)

Table 4. Air Quality Limit and Target Values, for PM10 and $PM_{2.5}$ as given in the EU Ambient Air Quality Directive and WHO Air Quality Guidelines (Source: Department for Environment Food % Rural Affairs, 2012).

Size Fraction	Averaging period	EU Air Quality Directive (Objective and legal nature and concentration)	WHO guidelines
$PM_{2.5}$	1 day	25 μg/m^3	25 μg/m^3
$PM_{2.5}$	Calendar year	25 μg/m^3	10 μg/m^3

As shown in Table 4, the EU limit values follow EU parameters, which must not be surpassed and have been made obligatory by EU Directives to take all necessary measures to maintain the set values.

London and New York

Drilling down from cases of the BRICs and the EU, London and New York have been chosen as particularly interesting areas for study. London and New York, the two big cities of HICs (United Kingdom and United States of America) have been recognised as the busiest cities in the world with increasing population growth and rapid urbanisation. Such urbanisation has exposed people to heavy traffic flow; and growing rates of AD are associated with the traffic situation in New York

and London, given the established statement that the risk of AD increases as people are exposed to more traffic where complex mixtures of environmental insults are present. This is dependent on the altitude of the city, availability of different fuels, types of vehicles involved, and emission control technologies [48]. Recent findings have highlighted that air pollution itself contributes to the development of AD in traffic settings, without interventions of any other factors such as road traffic noise [49]. 7% of dementia risk is augmented by living within 50 metres, 4% at 50-100 metres and 2% at 101-200 meters [50]. The correlation between AD and distance from heavy traffic roads seemed to have no significant effect after 200 meters [50]. It is important to also note that housing prices decrease nearer to main roads raising possible issues of social equity in relation to pollution exposure and AD risk. Traffic emissions account globally for 25% of ambient $PM_{2.5}$ [51]. The guideline for $PM_{2.5}$ in London is 25μg/m^3, to be achieved by 2020 [52]. It is reported that the current state reflects political and economic considerations in London, as well as health impacts [53].

New York City in the USA, where 5 million individuals are suffering from AD [54], is an ambitious area, attempting to achieve the goal of ‘cleanest air of any big city’. They have improved the air quality through clean air laws and regulations, yet there is still a high concentration of emissions from fuel combustion causing severe pollutants, leading to more than 3,000 deaths and 2,000 hospital admissions for lung and heart conditions and 6,000 emergency cases of asthma development [55]. It is reported that even a 10% reduction of $PM_{2.5}$ levels can prevent more than 200 hospital admissions and 300 premature deaths annually [56]. New York is a clear case which shows that improvements in air quality to a satisfactory level are impossible as air pollution still contributed to 6% of deaths despite improvements in air quality [57]. In December 2008, EPA revised the 24-hour average $PM_{2.5}$ standard, and designated the New York City Metropolitan Area as

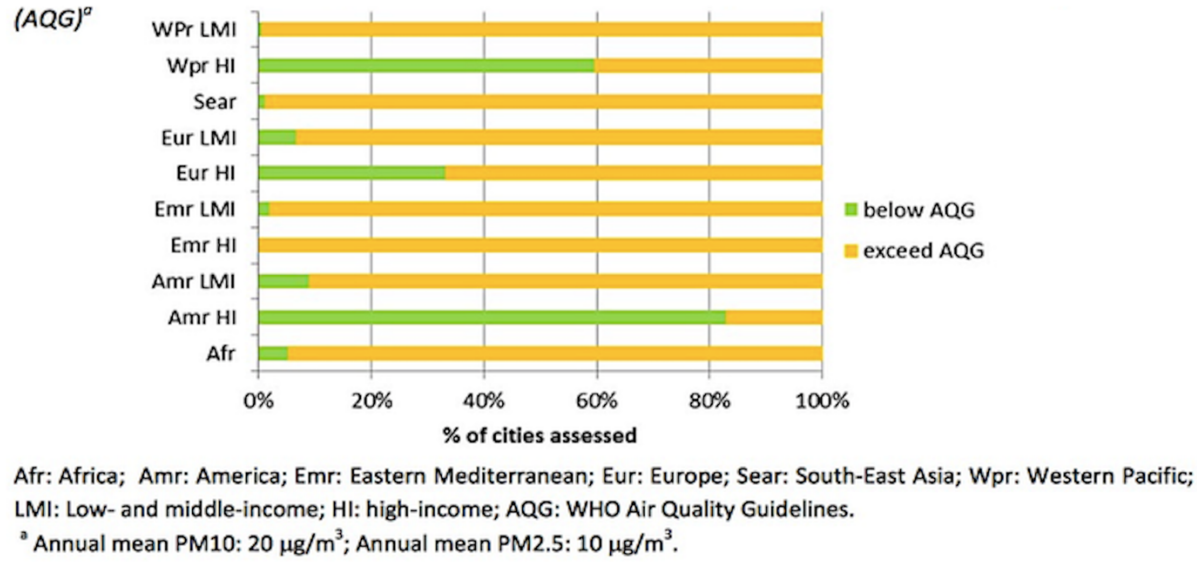
non-attainment. Non-attainment areas (NAAs) are defined as geographic regions, which have been designated as not meeting the NAAQS (National Ambient Air Quality Standards). New York was required to submit a State Implementation Plan (SIP) demonstrating attainment with the 24-hour standard by 2014 [58]. Table 5 shows National Ambient Air Quality Standards (NAAQS) of the USA [59].

Table 5. National Ambient Air Quality Standards (NAAQS) of the USA [59].

Fine Respirable Particulate Matter ($PM_{2.5}$)	**Primary (μg/m^3)**	**Secondary (μg/m^3)**
Average of 3 annual means	15	15
24-hour average	35	35

Differences in PM levels among countries

The World Health Organization (2016) investigated the level of $PM_{2.5}$ in specific areas to check whether they meet the WHO Air Quality Guidelines, which recommend annual mean values of 20 μg/m^3. The investigation sites were divided into HIC (High Income Countries), MIC (Mid-Income Countries), and LIC (Low Income Countries) within Western Pacific, South-East Asia, Europe, Eastern Mediterranean, America, and Africa [60] (Figure 4). WHO reported that only 16% of the assessed population globally were living in areas where $PM_{2.5}$ met the annual mean concentration limit. These figures rose to 27% with the application of interim target 3 (IT-3, 15μg/m^3 for $PM_{2.5}$) of the AQG, 46% for IT-2, and 56% for IT-1 [60].



Afr: Africa; Amr: America; Emr: Eastern Mediterranean; Eur: Europe; Sear: South-East Asia; Wpr: Western Pacific; LMI: Low- and middle-income; HI: high-income; AQG: WHO Air Quality Guidelines.
[a] Annual mean PM10: 20 µg/m^3; Annual mean PM2.5: 10 µg/m^3.

Figure 4. Annual mean PM of the assessed town and cities compared to the WHO Air Quality Guidelines (AQG). (Source: World Health Organization, 2016).

Figure 4 clearly displays the global trend of PM concentrations in each region, which seem to require improvements to meet the standards to ensure that air quality gives a lower impact on the causation of AD, the BRICs were studied as the samples of American, European, South-East Asian, and East Asian low/middle income countries. In Brazil, the national average $PM_{2.5}$ is 180 µg/m^3, which can be reduced to 80 µg/m^3 through avoiding heavy traffic areas and using firewood for cooking [61]. Annual average $PM_{2.5}$ concentrations 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 were expected in 2015 [62]. The data demonstrates that an estimated 40% of the Brazilian population had to live with air containing a higher concentration of $PM_{2.5}$ than the WHO annual air quality guideline [62]. Air pollution causes 49,000 deaths in Brazil each year, and about 50% of these deaths can be explained by the outdoor pollution, particularly in urban areas [62]. However, indoor air pollution results in the other 24,000 deaths, mainly because of cooking with wood and solid fuels, which especially affect rural communities [63]. As high as 20 million

individuals are living in areas which are 10-15 times higher than in cities in terms of the air pollution levels [62]. This value is 11-26 times greater than the WHO's recommendation, 10 μg/m^3. The government has set interim targets, which aim for improved cook stoves and 50% adoption of LPG (Liquefied petroleum gas), estimated to save 7,350 lives per year [62].

India reflects a very similar case, in which 7 out of the 9 selected areas [Pitamura, Mathura Road, Noida, Lodhi Rd, Pusa, Delhi, and Dheerur) were exposed to a concentration of $PM_{2.5}$, excessively beyond the suggested limit [64]. The Delhi Pollution Control Committee (DPCC) identified that 70% of a reduction in the annual average $PM_{2.5}$ was essential in Delhi to meet the annual standard of 40 μg/m^3, since the data from 2014 to 2017 illustrated 132μg/m^3, a concentration over three times the annual safe standard [65]. WHO has shown that 11 of the 12 cities with the worst $PM_{2.5}$ pollution are in India. Despite the WHO guideline value, the annual average concentration in Kanpur, known as the most polluted city in the world, is 319 μg/m^3. 2.5 million premature deaths could have been induced by pollution in 2015. India's pollution is attributed mainly to cars, cook-stoves coal and wood burning, dust storms, and forest fires.

Similarly, air pollution became a more prominent political and environmental issue when the US Embassy in China began publishing its readings in 2008 [66]. In 2013, there were 71 cities in China, which failed to satisfy the interim WHO target. Beijing, Tianjin and Hebei exceeded the $PM_{2.5}$ target concentrations by 15%, 25%, and 25% respectively before 2017. Beijing, which showed an annual average concentration of 73 μg/m^3 in 2016, has a target of 60 μg/m^3 for the next few years [66]. Beijing showed a constant decrease in the PM level from 89.5 μg/m^3 in 2013 to 85.9 μg/m^3 in 2014, and 80.6 μg/m^3 in 2015 [66]. However, it has been very debatable among experts whether Beijing will be able to meet this target within the given time.

In Russia, where the guideline of 25 μg/m^3 was adopted, the percentage of the population exposed to a level exceeding this guidance reached 89.7% in 2015, whilst the highest value over the last 25 years was 93.50% in 1990 and the lowest 88.07% in 2005 [67]. As Table 6 shows, considerable population percentages in the BRICs have been exposed to high levels of $PM_{2.5}$ [62].

Table 6. Population living in areas where $PM_{2.5}$ levels exceed the WHO guideline set value in 2015-2016 [62].

$PM_{2.5}$ Air Pollution	
BRIC country	**% of population exposed to levels exceeding the WHO guideline**
Brazil	55.8
Russia	89.66
India	99.99
China	100

However, unlike the BRICs, which are on the verge of developed status, HICs show a different approach 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.

Figure 5 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.

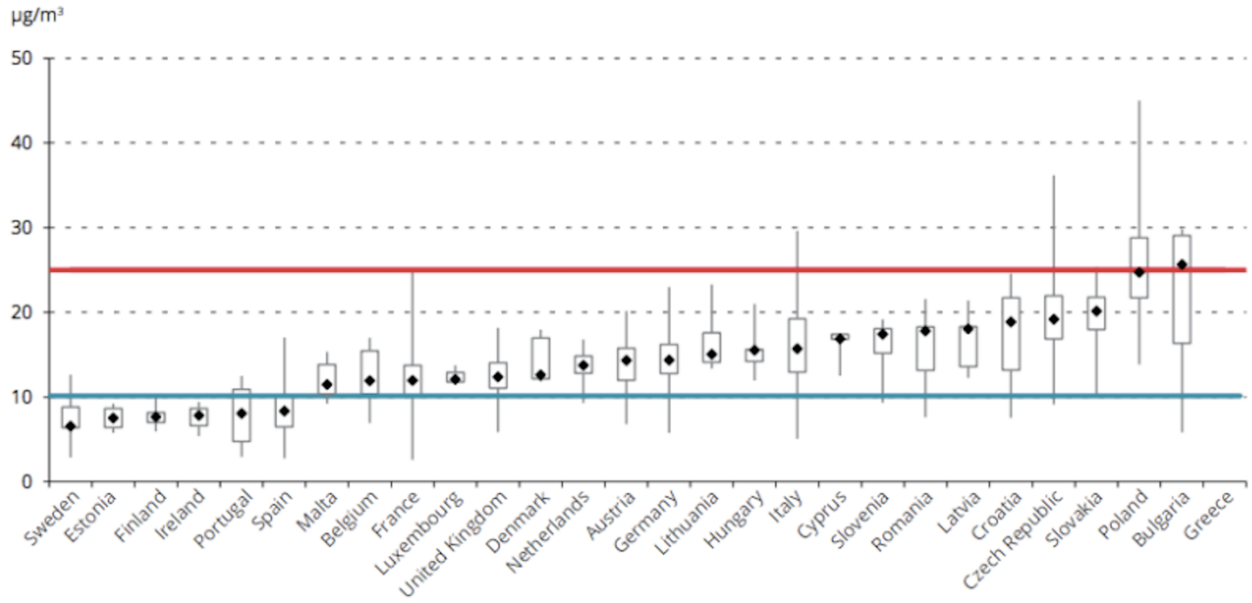


Figure 5. $PM_{2.5}$ concentrations in relation to the target value in 2014. Each country has been given the lowest, median, and highest values at the stations, with the box plots representing the 25th and 75th percentiles. The red line defines the target value set by EU legislation, and the blue line shows the WHO standard. (Source: European Environment Agency, 2016).

Figure 5 demonstrates a decrease in the $PM_{2.5}$ concentration average between 2006 and 2014. It is hard to draw definite conclusions from the trend shown in the data, yet one can observe that there has been a reduction in $PM_{2.5}$ concentrations in general, which is a positive sign in terms of the association with AD as well. Interestingly, Figure 5 indicates that HICs, located in the west of Europe, have a tendency of showing lower concentrations of $PM_{2.5}$, whilst countries with lower Gross National Income (GNI) in the east have higher concentrations [68]. This confirms that there is a relationship between economic activities and the PM concentrations, which will be explored further later in the paper. It suggests that it would be difficult for some Lower Income Countries (LICs) to limit their activities to reduce PM concentrations, and hence it would be difficult for all countries to follow the PM guideline values.

The average $PM_{2.5}$ level in London in August 2018 was 58 $\mu g/m^3$ [69], excessively higher than the guideline value. It has been acknowledged explicitly that "Progress in dealing with PM emissions will stall in 2020 once exhaust emissions are significantly reduced. London is currently far from

achieving WHO health-based limits for $PM_{2.5}$. One of the best ways to do this would be to reduce the number of vehicle kilometres by supporting a mode shift to walking, cycling and public transport. It will also be necessary to address wood burning related emissions, which evidence suggests are a significant source of emissions, particularly on some of the most polluted days" [70]. Unlike London, New York showed an annual mean of $PM_{2.5}$ concentration of 24 μg/ m3 [69]. A study of adults aged between 20 to 65 years estimated the association between $PM_{2.5}$ and daily hospital admissions: there was a 2.2% increase in these admissions for every 10 $\mu g/m^3$ increase in average daily $PM_{2.5}$ [56].

Developed countries are prepared to combat pollution given their resources and technologies, and have been putting efforts to reduce pollution due to the health risks and potential impact of climate change. However, in developing countries where economics are driven by funds generated from natural sources and exploitation because of the less developed third industry, exploitation and processing of such resources lead to air pollution. For example, for Nigeria to continue its current economic growth path and attempt to reduce poverty, oil exploration and production have to be their dominant economic activity [71]. Industrialisation asks for massive use of energy resources, which could cause pollution and environmental degradation. For example, China would not have fulfilled such impressive economic growth in recent years if they had cared about pollution [71]. Other developed countries, such as those in the OECD, may seek to focus on environmental sustainability, only after achieving substantial growth and an improvement in the standard of living.

As shown in Table 7, in countries there is a direct correlation between economic development and air pollution (concentrations of $PM_{2.5}$). The measure of economic development refers to the HDI index which considers the GNI per capita value to evaluate economic development [72]. The level

of air pollution has been assessed through the mean annual concentration of $PM_{2.5}$ based on the World Bank data in 2016 [73]. One aspect of note is that developing countries with relatively low GNI per capita showed increases in $PM_{2.5}$ from 1990 to 2016, while developed countries showed decreases. There is also a general trend that developed countries show lower $PM_{2.5}$ annual level compared to developing countries.

Table 7. The relationship between air pollution (level of $PM_{2.5}$) and economic development in 18 selected countries from all regions.

Country	$PM_{2.5}$ air pollution, mean annual concentration (micrograms per cubic meter) in 1990	$PM_{2.5}$ air pollution, mean annual concentration (micrograms per cubic meter) in 2016	GNI per capita ($)	HDI value
Norway	11	8	67614	0.949
Germany	17	13	56364	0.926
United States	11	9	53245	0.920
Australia	7	6	42,822	0.939
Belgium	20	16	41,243	0.896
France	14	12	38085	0.897
United Kingdom	14	12	37931	80.800
Japan	13	13	37268	83.700
Russia	2	16	23,286	0.804
Brazil	15	13	14145	0.754
Algeria	34	37	13,533	0.745
China	48	56	13,345	0.738
India	60	76	5,663	0.624
Congo, Dem. Rep.	48	56	5,503	0.592
Nigeria	81	122	5,443	0.527
Afghanistan	61	63	1871	0.479
Ethiopia	36	50	1,523	0.448

Alzheimer's Disease incidence and prevalence: Differences between developed and developing countries.

Each year, the World Bank publishes a revised list of country income levels, dividing economies into four groups according to their Gross National Income (GNI) per capita. This index of average income is a general indicator of development status; people living in countries with higher GNI per capita tend to have longer life expectancies, higher literacy rates, better access to safe water, and lower infant mortality rates. The four groups are low income countries (LIC), lower - middle income countries (L-MIC), upper- middle income countries (U-MIC) and high-income countries (HIC). In 2009 the income thresholds were; LIC, $995 or less; and HIC: $12,196 or more [74].

There were 46.8 million people worldwide suffering from dementia in 2015, and the number is predicted to double every 20 years – projected to reach 75 million in 2030 and 131.5 million in 2050. It has been shown that 58% of AD patients already live in LICs or MICs – however, this value will increase to 68% by 2050, primarily due to the increase in elderly populations despite the stunted growth in health care services and other standard of living in China, India, and their south Asian and western Pacific neighbours [75]. Research indicates that a majority of people with AD do not receive a formal diagnosis. In HICs, only 20-50% of AD cases were recognised and documented in primary care, while this 'treatment gap' was much more serious in LICs and MICs. For example, 90% of people with AD remained undiagnosed in India [75].

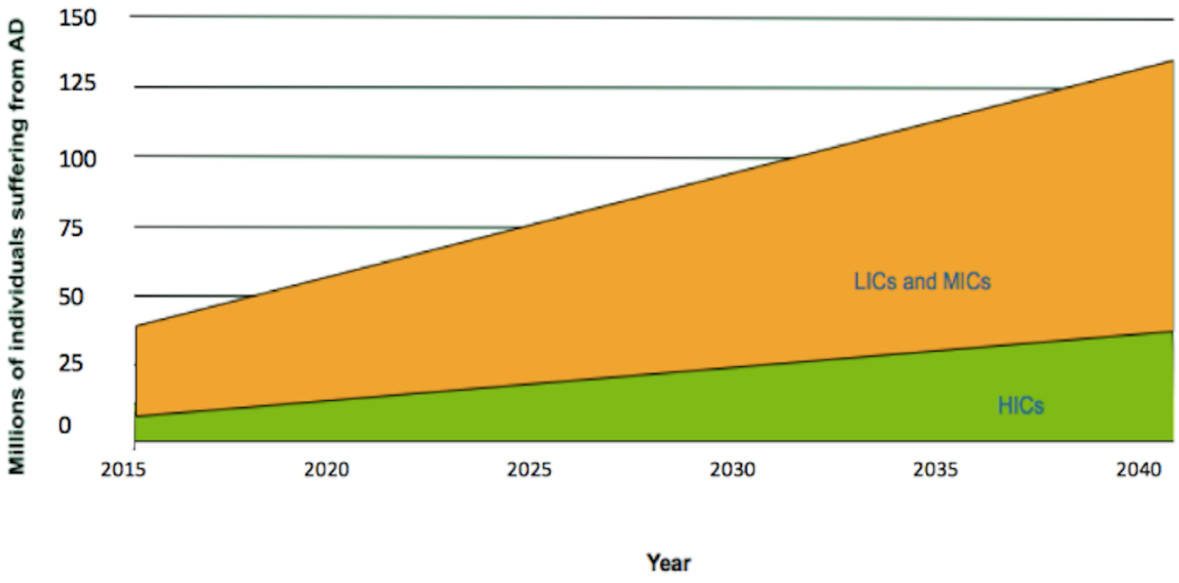


Figure 6. Number of individuals with AD in countries of varying GNI.

Table 7 highlights that the prevalence of AD tends to be higher in developing countries (LICs and L-MICs) [74].

Table 7. Numbers of individuals with AD (millions) according to the 2015 World Bank income classification.

World Bank Income Group	Number of Individuals with AD (millions)						
	2015	**2020**	**2025**	**2030**	**2035**	**2040**	**2045**
LIC	1.19	1.42	1.68	2.00	2.41	2.90	3.55
L-MIC	9.77	11.52	13.72	16.35	19.48	23.12	27.18
U-MIC	16.32	19.36	23.33	28.39	34.28	40.43	46.90
HIC	19.50	21.97	24.73	27.95	31.72	35.71	39.14
World	46.78	54.27	63.45	74.69	87.88	102.15	116.78

According to a study by Prince et al. (2012), it has been found that AD, which was thought of as a scourge of the developed world due to the aging population, occurs at an even higher rate in

developing countries. Earlier studies claimed that less developed countries tend to show lower prevalence and incidence of AD than in the US and Europe [76–78]. However, recent findings revealed that LICs tend to show 1.8% of higher AD incidence than HICs [79]. A shift in the developing countries' populations toward aging, as well as low education and undercounting may be responsible. The cost of AD to society is the value of all services and goods, which are used for prevention, diagnosis, treatment and other means of coping with AD. Economic costs of AD are significant for health systems, affecting a wide range of people, including individuals, families, and carers. Costs are divided into direct and indirect costs; direct such as days spent in hospital, drugs, medical services, while the indirect costs covers money that has been spent implicitly, as loss of income by the patient. This could lead to a formation of a negative-multiplier effect, where poor communities with less socio-economically developed health services and poor governmental support, as well as the poor prevention and investment of AD would lead to a higher number of patients suffering from AD. This also infers that more money will be spent to care for them both directly and indirectly, which potentially means a greater percentage of tax to the government will be spent on care, instead of improving other services and facilities nationally.

Differences in low educational levels between developed and developing countries.

Socio-economic factors contribute to the risk of developing AD. Low educational level is a well-recognised risk factor. Educational exposure is considered to improve cognitive reserve through neuroplasticity and production of more complex neural networks, leading to the ability to compensate for greater degrees of neuropathology in later life [80]. It was estimated that every one additional year of education can result in 11% reduction in the risk of developing AD [81].

In this study, in order to assess the difference in education levels between developed and developing countries, the Human Development Index (HDI) was used. HDI takes various factors into

consideration including life expectancy, expected years of schooling, mean years of schooling and GNI (Gross National Income) per capita to assess socio-economic status. The higher the HDI, the higher the level of development is considered to be [72]. Table 8 depicts a trend that the more developed the country is in terms of a higher HDI rank, the higher the expected years of schooling and the mean years of schooling are. Developed countries show a proportionately high tendency of better education than developing countries.

Table 8. Differences in educational levels between developing and developed countries based on the HDI values and ranks [72].

HDI Rank	Country	HDI value	Expected years of schooling	Mean years of actual schooling
1	Norway	0.949	17.7	12.7
2	Australia	0.939	20.4	13.2
3	Switzerland	0.939	16.0	13.4
4	Germany	0.926	17.1	12.7
5	Denmark	0.925	19.2	11.6
10	United States	0.920	16.5	13.2
12	Hong Kong, China (SAR)	0.917	15.7	11.6
13	New Zealand	0.915	19.2	12.5
14	Sweden	0.913	16.1	12.3
15	Liechtenstein	0.912	14.6	12.4
16	United Kingdom	0.909	16.3	13.3
17	Japan	0.903	15.3	12.5
18	Korea (Republic of)	0.901	16.6	12.2
30	Brunei Darussalam	0.865	14.9	9.0
30	Estonia	0.865	16.5	12.5
32	Andorra	0.858	13.5	10.3

33	Cyprus	0.856	14.3	11.7
33	Malta	0.856	14.6	11.3
66	Costa Rica	0.776	14.2	8.7
66	Serbia	0.776	14.4	10.8
68	Cuba	0.775	13.9	11.8
69	Iran (Islamic Republic of)	0.774	14.8	8.8
70	Georgia	0.769	13.9	12.2
110	Paraguay	0.693	12.3	8.1
111	Egypt	0.691	13.1	7.1
111	Turkmenistan	0.691	10.8	9.9
113	Indonesia	0.689	12.9	7.9
114	Palestine, State of	0.684	12.8	8.9
148	Swaziland	0.541	11.4	6.8
149	Syrian Arab Republic	0.536	9.0	5.1
150	Angola	0.533	11.4	5.0
151	Tanzania (United Republic of)	0.531	8.9	5.8
152	Nigeria	0.527	10	6.0

A low level of socio-economic development, which results in poor education, is strongly associated with the poor intellectual and cognitive development. Research shows that children from developing countries developed academic skills slower than children from HICs, due to the poor cognitive development, as well as slow progress in acquiring language, memory and socio-emotional processing [82]. Low educational level from developing countries did not only impact the children, but also the elderly population. The protective effect of education and other socioeconomic factors established in developed countries is interesting as it emphasizes the

importance of background on AD. A study by American Academy of Neurology (2007) has asserted that people who do not complete high school are at a higher risk of developing AD compared to people who have undergone more education, regardless of lifestyle choices and characteristics, including smoking, income, occupation, and physical activity [83]. The authors found out that a 40% and 80% lower risk of developing AD were noticed among the population who completed a medium education level and a high education level respectively, based on an experiment with 1,388 participants in Finland [83]. This could be attributed to by unhealthy lifestyles and low cognitive reserve, which is the brain's capacity to maintain function in spite of damage. A study on the rural Chinese island of Kinmen, also demonstrated an increase in AD incidence rates as the population turned 60 because of their only one-year of median level of education [84]. This suggests lack of education and illiteracy are related to developing AD sooner.

AD cures and treatments

The currently available treatments which can help the development of AD cures include drugs, which alleviate the symptoms of AD or slow down the progression of developing the illness – and these drugs are often limited to mainly developed countries because of the restricted expenditure developing countries can spend due to other priorities. The main medications available include acetylcholinesterase inhibitors and NMDA (N-Methyl-D-aspartate) receptor antagonists, which restore reduced levels of acetylcholine. This helps to deliver messages between certain nerve cells and prevent the hypofunction of N-Methyl-D-aspartate receptor that can trigger memory deficits [85]. Nevertheless, treatments could only help manage the disease rather than eliminating it altogether. Even though no cure is available for AD now, it is proposed that the first drug may be available within 4 years for the cure [86]. Liraglutide, mainly used to treat diabetes currently through binding to the same receptors, as does endogenous metabolic hormone GLP-1 to induce

insulin secretion, can prevent the farther progress of AD and improve mental function [86]. Furthermore, various diagnosis techniques have been investigated, such as the use of surface plasmon resonance, which can assess the patient's exosomes which can provide the platform for the AD detection, as exosomes can be extracted via urine and blood. Exosomes suffering from AD would display their unique biomarker of CD63, along with the hint of accumulated amyloid beta [87–89]. Contrary to the number of individuals having 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 only £90 million [90]. Also, while the US government spent $200 billion on AD care in 2016, its spending was less than 1% of that figure on research [91]. This implies to be the factor for the slow development of medications, despite AD continuing to be the World's 6th leading cause of death [92]. The conclusion of this argument points towards the need for further research and funding for the medication of AD.

An integrated multi-level model for predicting Alzheimer's Disease

In undertaking this study, the following certitude has been established where $PM_{2.5}$ exposures can lead to AD, not only via the direct route, which is the olfactory mucosa, but also through the neuro-inflammatory responses. Air pollution levels are significantly greater in the BRICs and other socio-economically developing countries compared to U.S. and EU levels [93]. 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.

A higher incidence of AD has been shown, corresponding to the low socio-economic development in developing countries, which have been defined as either L-MICs (Low-middle income countries) or developing world of low HDI values. These developing areas are more likely to be exposed to environments where economic activities are prioritised over the air quality improvement. Figure 7

is drawn based on Table 7, which shows the correlation between the mean annual exposure of $PM_{2.5}$ and economic development (GNI per capita). This figure highlights that the higher the GNI per capita in HICs, the lower the $PM_{2.5}$ exposure which carries a possibility of developing AD. Figure 7 indicates that HICs are on the right side of the graph where the GNI per capita exceeds about $ 35,000, and also countries (OECDs) which are also appointed to the G20 because of their strong economies. They show a relatively low exposure to $PM_{2.5}$, of 20 $\mu g/m^3$ or below. This trend is clearly shown because of the logarithmic curve, which goes down along the increase in GNI per capita.

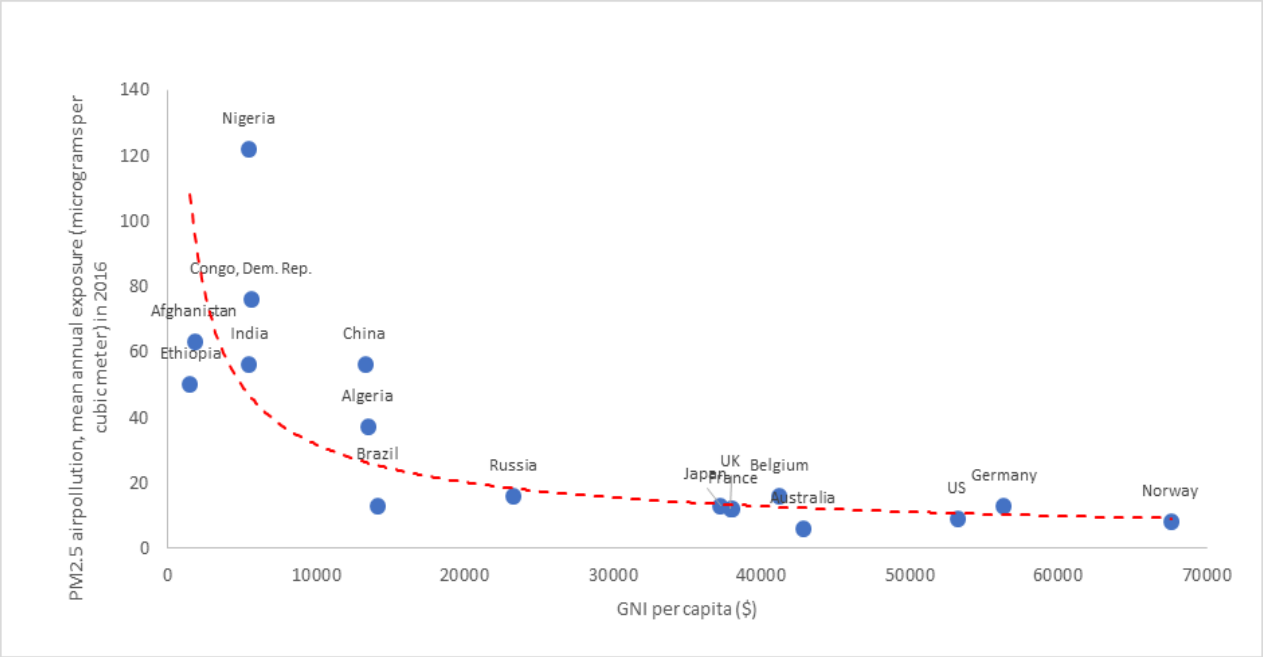


Figure 7. Mean annual $PM_{2.5}$ exposure vs GNI per capita for both HCI's and OECD countries with strong economies.

Figure 8 is the simplified version of the three aspects – $PM_{2.5}$ prevalence, low socio-economic development, and risk of developing AD – to illustrate the point made throughout the paper that economically disadvantaged individuals are at a particularly high risk of experiencing more inflammation-related health problems, especially Alzheimer's disease, compared to individuals in

economically advantageous circumstances, 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.

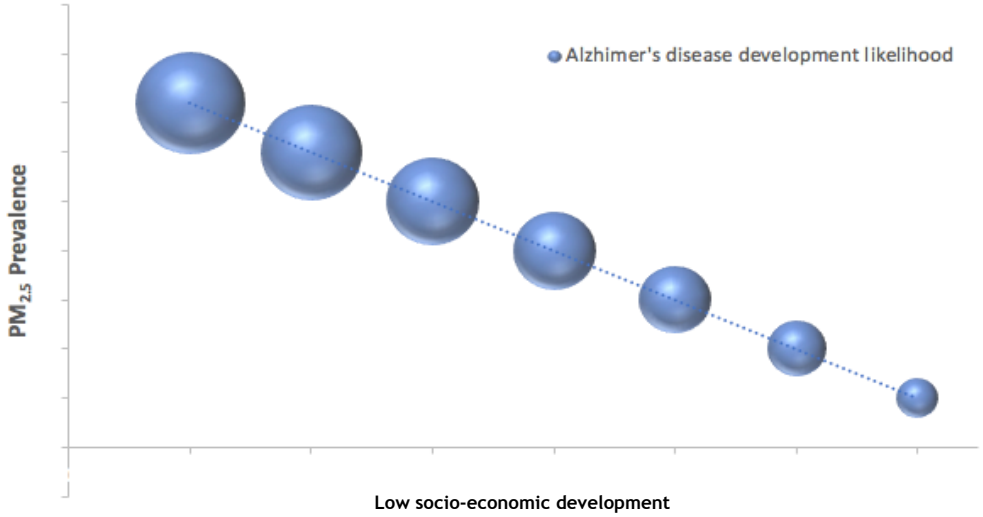


Figure 8. An integrated, multi-level model of the interactions between air pollution, socio-economic development, and Alzheimer's disease.

Our model shows a pathway through which environmental factors (i.e. $PM_{2.5}$ exposure) and socio-economic factors (based on GNI per capita and HDI values) interact to raise the risk of AD. The X-axis denotes the level of socio-economic development, ranging from the household income to the national scale. The Y-axis displays the $PM_{2.5}$ exposure prevalence in percentage (%). The blue circles denote the likelihood of developing AD, which is related to the relationship between the $PM_{2.5}$ prevalence and socio-economic development. The graph proposes that the lower the socio-economic development, the higher the $PM_{2.5}$ exposure one can experience, which can thus lead to a higher risk of developing AD. In Figure 8, a higher prevalence of AD has been demonstrated also with a lower level of education in developing countries, which leads to a hypothesis that low recognition of AD, as well as public health education towards prevention and treatment of AD could

be the reason for a higher AD. At the same time, unhealthier lifestyles and low cognitive reserve based on low educational level could be the factors contributing to a higher likelihood of developing AD. There is a correlation between the development of AD and mean years of schooling, which indicates the nationally supported educational level for the population could improve the socio-economic level, thus impacting on the prevalence of AD. This notion has been indicated through the expression of data based on 34 nations, in Figure 9.

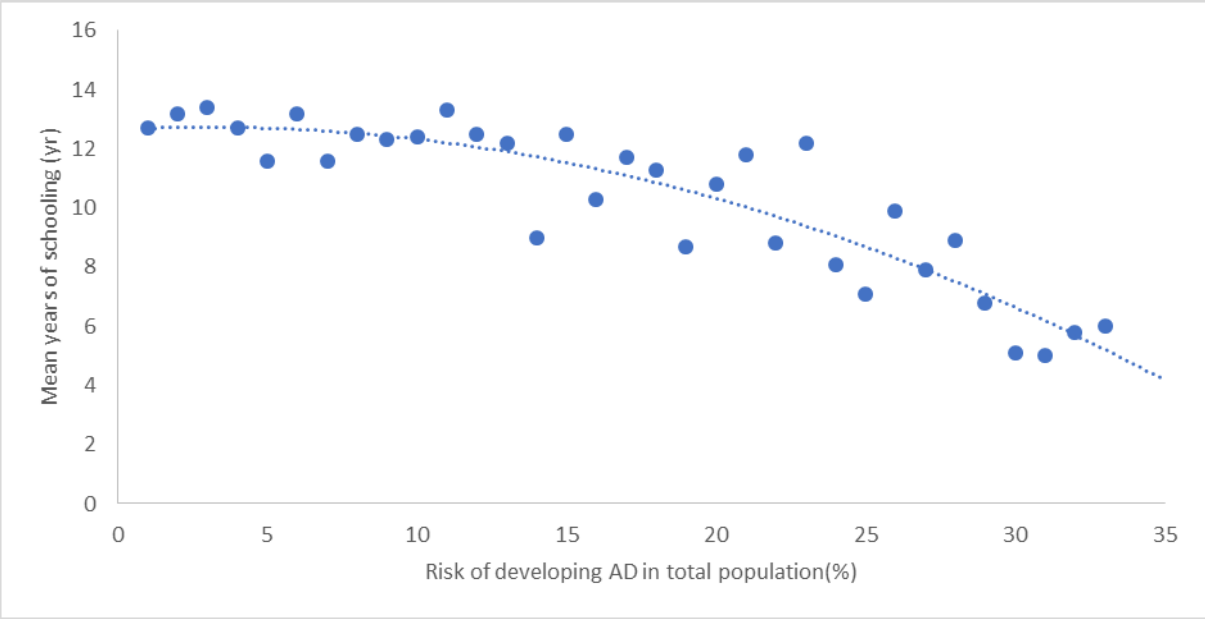


Figure 9. Correlation between level of schooling and risk of developing AD in total population.

The model shows an interaction between the mean years of schooling which represents the educational level of countries for socio-economic levels and the risk of developing AD in total population. As showed in Figure 9, each blue dot represents each country involved in the data collection, ranging from HICs to LICs, and a trendline has been produced. Hence, Figure 8 and 9 can be upgraded to produce Figure 10, by including the level of education, Figure 10 shows that a lower socio-economic development can lead to, or co-exist with a low educational level, which can

be associated with a high $PM_{2.5}$ exposure, potentially resulting in Alzheimer's disease, either solely because of the air pollution, low educational levels, or both.

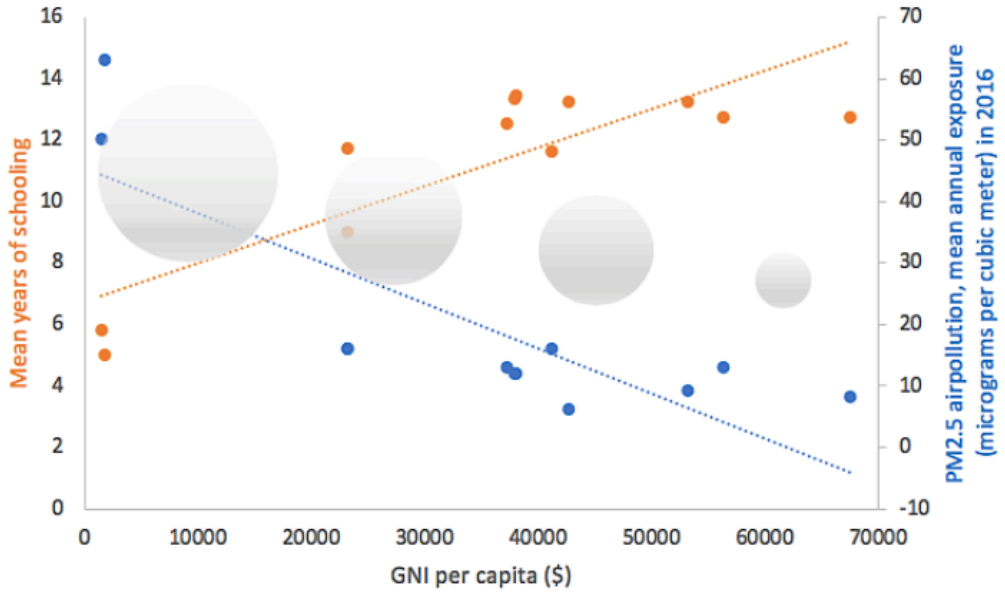


Figure 10. Interaction between level of schooling, GNI per capita and $PM_{2.5}$ levels.

The model shows an interaction between economic situations based on GNI per capita, social aspects based on mean years of schooling for education, $PM_{2.5}$ exposure, and the likelihood of developing AD. The size of the grey circles represent the risk of developing AD along with the decreased years of schooling and higher $PM_{2.5}$ air pollution exposure. Each orange and blue dots represent the levels of countries listed in Tables 7 and 8. The model depicts a pathway through which specific socio-economic factors (poor residential conditions and geographical sites, low educational level) and environmental factors (i.e. air pollution exposure) interact to increase the risk of developing Alzheimer's disease. A variety of literature in the field supports the association between low educational level and AD, whilst the association between $PM_{2.5}$ and AD is not as strong. However, the graphs suggest that both low educational level and $PM_{2.5}$ in the list of

countries by GNI per capita show a corresponding rend, and hence may be the important socio-economic factors, which contribute to the development of AD.

An integrated multi-level intervention to target Alzheimer's Disease

Our model suggests four points should be considered throughout: 1) combatting air pollution is more likely to draw political attention; 2) applying wide-ranging environmental regulations to developing communities may lead to some economic and social inequities relative to HICs; 3) there is issue of social justice to be considered for less economically developed countries; and 4) improvement in the education system in developing communities at this point can contribute to resolving the AD issue and socio-economic inequalities. We propose that as cures are a big unknown, there is still a need to find and research them, yet we should pursue dealing with all the other issues as a 'prevention rather than cure' approach. The world would be evidently better if all countries adhered to strict environmental policies to reduce $PM_{2.5}$ in the atmosphere. This way, restricting economic activities may be able to prevent deaths from AD through reducing the PM concentrations in the air – nevertheless, it will have an effect on the lifestyles of individuals as well as the performance of firms, leading to serious societal consequences. For instance, China's huge capital iron and steel work has been their primary source of pollution. Restricting this huge-scale work will lessen the PM level at the cost of 40,000 jobs [94]. In addition, China's economic progress is powered by cheap coal firmly, despite its contribution to the $PM_{2.5}$ concentration level. Coal combustion accounts for 40% of the total national level and up to 50% in Sichuan Basin [94]. The equal application of rigorous environmental policies would cause obstacles to economic growth and a risk to political stability. Nevertheless, it would be disingenuous to suggest that the Chinese government had not been aware of this until recently, and is only starting to take steps to address these issues.

A focus on the cut-down of $PM_{2.5}$ would not be an adequate solution due to socio-economic elements, which are also important to consider. The ethical issue arises whether it is equitable to impose tight environmental regulations on countries that have not yet undergone and benefitted from industrialization. It is usually argued that it is hypocritical that HICs demand LICs to prioritise environmental protection, as HICs damaged their environment through industrialization [95]. In any case, as they become more affluent, they seem to become more concerned about the environment and reach the position where they can finally afford investment towards the prevention of 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 developed countries such as Europe or the USA. Restraining the development of profitable yet polluting industries, such as oil refineries and steel, can force these countries to linger economically backwards [95]. 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 [94]. 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 [94]. 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. We should make 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.

Along with the effort to reduce $PM_{2.5}$, we should focus on the association between the low education level and risk of developing AD, which is more evident so far based on the literary work. There are ways in which low educational level can be addressed. It is important that actions are taken to improve the quality of education in less developed societies, not only the LICs but also small communities in rural areas of relatively developed countries. The three main principals to improve the quality of education include: supply-side interventions, behavioural interventions, and participatory and community management interventions [96]. Figure 11 summarises the strategies of improving education, based on Niño-Zarazúa's proposal [96].

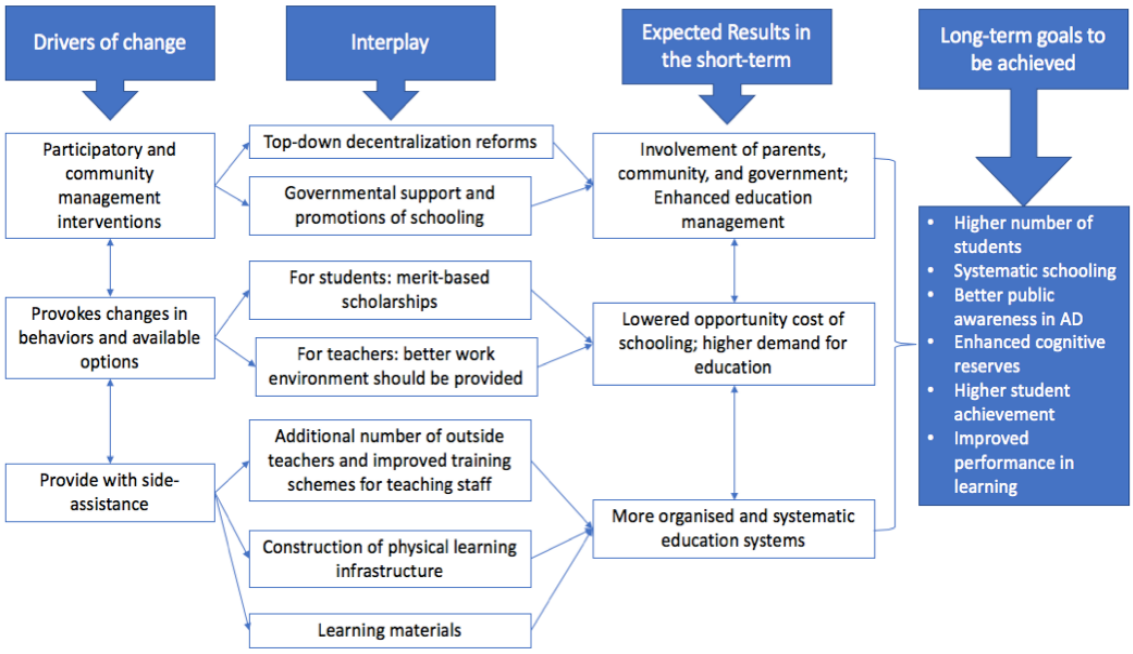


Figure 11. The three types of intervention strategies which can be applied to improve the quality of education in developing communities. (Source: Niño-Zarazúa modified [96]).

Education not only for the purposes of improving one's cognitive senses, but also for the purposes of improving awareness about AD through public health education is important. In order to reduce discrimination and possible social exclusion, and to encourage an early or timely diagnosis and approach to subsequent care, several actions are needed in an integrated, multi-level AD plan. These range from information dissemination and educational awareness campaigns, to establishing a national helpline and website with information, as well as advice at a local level. Some plans considered as far as to organise regional conferences (for example, France) to increase awareness of AD and even develop a basis to check public knowledge and attitudes through population surveys [97].

CONCLUSION

Alzheimer's disease is moving toward a category, which will likely classify AD to be preventable and curable in the next future. Air pollution is one of the leading factors of development of AD. This paper attempts to theorise a model for minimising the impact of AD and slow down the AD progression through prevention, by understanding its causal relationship with air pollution and other socio-economic factors such as the economic situation and level of education provided. Three associations are discovered and highlighted in undertaking this study: 1) A correlation between air pollution and development of AD; 2) a correlation between the prevalence of AD and economic development; 3) a correlation between social aspect, which is the lower level of education and development of AD. It is debatable whether the casual relationship between a high level of $PM_{2.5}$ and prevalence of AD is more evident than the causal relationship between the prevalence of AD and low educational level. While there have been numerous studies supporting the association between low educational level and higher chance of developing AD, studies confirming the link between $PM_{2.5}$ and AD are currently limited. It is plausible that low education is only a marker of

general social disadvantage, which is difficult to separate from other socioeconomic factors related to AD, like rural residence. Not only AD, but other markers of cognitive reserve are suggested in settings where access to education is low for the population [98]. Stronger associations were shown between the lower level of education and AD development, based on present studies. Nevertheless, we expect future studies to highlight the significance of the exposure of $PM_{2.5}$ as a contributor to the development of AD. In the meanwhile, we have developed a new interdisciplinary theoretical model based on neurobiology, sociology of medicine and eco-political science to understand Alzheimer's disease and other forms of dementia, to move forward and lead to an improvement to actionable policies.

Strengths and Limitations

It is inevitable that this study has some limitations. Firstly, since the conclusion has been drawn 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 unavailable at the time of this research. In addition, further epidemiological research about differences in incidence of AD between developing and developed countries is required to understand the causal relationship between AD and socio-economic aspects more clearly. The concept of improving the economy as well as education is generalised throughout the study, as inequalities are present within the developing countries where well-organised education systems are prepared in some sites within those countries. Nonetheless, despite these uncertainties and limitations, the results of this study provide important indications of likely impacts that can be used to inform policy decisions. Indeed,

aalthough our model does not include other well-recognized causes of AD and needs to be tested by further in-depth epidemiological studies, more holistic and realistic views on the current approaches will allow this field to move forward and lead to a more effective strategy against AD.

References

1. Adler NE, Stewart J. Health disparities across the lifespan: Meaning, methods, and mechanisms. Ann N Y Acad Sci [Internet]. 2010 Feb [cited 2018 Sep 19];1186(1):5–23. Available from: http://www.ncbi.nlm.nih.gov/pubmed/20201865.
2. Braveman P, Gottlieb L. The Social Determinants of Health: It's Time to Consider the Causes of the Causes. Public Health Rep [Internet]. 2014 Jan [cited 2018 Sep 19];129(1_suppl2):19–31. Available from: http://www.ncbi.nlm.nih.gov/pubmed/24385661.
3. Frieden TR, Harold Jaffe DW, Moolenaar RL, Leahy MA, Martinroe JC, Spriggs SR, et al. CDC Health Disparities and Inequalities Report-United States, 2013 Supplement Morbidity and Mortality Weekly Report Supplement Centers for Disease Control and Prevention MMWR Editorial and Production Staff MMWR Editorial Board [Internet]. 2013 [cited 2018 Sep 19]. Available from: https://www.cdc.gov/mmwr/pdf/other/su6203.pdf.
4. World Health Organisation. Ambient Air Pollution: A Global Assessment of Exposure and Burden of Disease. Geneva, Switzerland; 2016.
5. HEI. State of Global Air [Internet]. 2017 [cited 2018 Sep 19]. Available from: https://www.stateofglobalair.org/sites/default/files/SOGA2017_report.pdf.
6. Streit W. Microglial Activation and Neuroinflammation in Alzheimer's Disease: A Critical Examination of Recent History. Front Aging Neurosci. 2010;2(22):1–5.
7. Moulton, PV; Yang W. Air Pollution, Oxidative Stress, and Alzheimer's Disease. J Env

Public Heal. 2012.

8. Alzheimer's Association. Dementia Types | Symptoms, Diagnosis, Causes, Treatments [Internet]. 2018 [cited 2018 Sep 19]. Available from: https://www.alz.org/alzheimers-dementia/what-is-dementia/types-of-dementia.
9. Tate M, Cooper-Knock J, Hunter Z, Wood E. Neurology and clinical neuroanatomy on the move.
10. Beyreuther K, Masters CL. Amyloid precursor protein (APP) and beta A4 amyloid in the etiology of Alzheimer's disease: precursor-product relationships in the derangement of neuronal function. Brain Pathol [Internet]. 1991 Jul [cited 2018 Sep 19];1(4):241–251. Available from: http://www.ncbi.nlm.nih.gov/pubmed/1669714.
11. Hardy J, Allsop D. Amyloid deposition as the central event in the aetiology of Alzheimer's disease. Trends Pharmacol Sci [Internet]. 1991 Oct [cited 2018 Sep 19];12(10):383–388. Available from: http://www.ncbi.nlm.nih.gov/pubmed/1763432.
12. Selkoe DJ. The molecular pathology of Alzheimer's disease. Neuron [Internet]. 1991 Apr [cited 2018 Sep 19];6(4):487–498. Available from: http://www.ncbi.nlm.nih.gov/pubmed/1673054.
13. Block ML, Calderón-Garcidueñas L. Air pollution: mechanisms of neuroinflammation and CNS disease. Trends Neurosci [Internet]. 2009 Sep [cited 2018 Sep 19];32(9):506–516. Available from: http://www.ncbi.nlm.nih.gov/pubmed/19716187.
14. Miller G, Chen E. Unfavorable socioeconomic conditions in early life presage expression of proinflammatory phenotype in adolesccence. Psychosom Med. 2007;69:402–409.
15. Jung C-R, Lin Y-T, Hwang B-F. Ozone, Particulate Matter, and Newly Diagnosed Alzheimer's Disease: A Population-Based Cohort Study in Taiwan. J Alzheimer's Dis [Internet]. 2015 Jan 22 [cited 2018 Sep 8];44(2):573–584. Available from: http://

www.ncbi.nlm.nih.gov/pubmed/25310992.

16. Andreas Becker / ara. Economic growth vs. environmental protection | Globalization | DW | 16.06.2013 [Internet]. 2013 [cited 2018 Sep 19]. Available from: https://www.dw.com/en/economic-growth-vs-environmental-protection/a-16878236.
17. Sciences. NRC (US) C on EENRC (US) C on L. 3 Exposure Assessment in Environmental Epidemiology. In: Environmental Epidemiology: Volume 2: Use of the Gray Literature and Other Data in Environmental Epidemiology. 1997.
18. Imai K, Tingley D, Yamamoto T. Experimental designs for identifying causal mechanisms [Internet]. Vol. 176, J. R. Statist. Soc. A. 2012 [cited 2018 Sep 19]. Available from: https://imai.fas.harvard.edu/research/files/Design.pdf.
19. Yang W, Omaye S. Air pollutants, oxidative stress and human health. J Environ Public Health. 2009;674(1–2):45–54.
20. Dresner S. The principles of sustainability. 2nd Editio. London: Routledge; 2012.
21. Bose S, Diette GB. Health Disparities Related to Environmental Air Quality. In: Health Disparities in Respiratory Medicine. Humana Press, Cham; 2016. p. 41–58.
22. TNN. 70% cut in PM2.5 levels needed [Internet]. 2017 [cited 2017 Feb 28]. Available from: http://timesofindia.indiatimes.com/city/delhi/70-cut-in-pm2-5-levels-needed/articleshow/57381301.cms.
23. Oberdörster G, Elder A, Rinderknecht A. Nanoparticles and the brain: cause for concern?. J Nanosci Nanotechnol [Internet]. 2009 Aug [cited 2018 Sep 19];9(8):4996–5007. Available from: http://www.ncbi.nlm.nih.gov/pubmed/19928180.
24. Oberdörster G, Sharp Z, Atudorei V, Elder A, Gelein R, Kreyling W, et al. Translocation of Inhaled Ultrafine Particles to the Brain. Inhal Toxicol [Internet]. 2004 Jan [cited 2018 Sep 19];16(6–7):437–45. Available from: http://www.ncbi.nlm.nih.gov/pubmed/15204759.

25. Craig P, Dieppe P, Macintyre S, Michie S, Nazareth I, Petticrew M, et al. Developing and evaluating complex interventions: the new Medical Research Council guidance. BMJ [Internet]. 2008 Sep 29 [cited 2018 Sep 19];337:a1655. Available from: http://www.ncbi.nlm.nih.gov/pubmed/18824488.

26. Mazzoli-Rocha F, dos Santos AN, Fernandes S, Ferreira Normando VM, Malm O, Nascimento Saldiva PH, et al. Pulmonary function and histological impairment in mice after acute exposure to aluminum dust. Inhal Toxicol [Internet]. 2010 Aug 14 [cited 2018 Sep 19]; 22(10):861–867. Available from: http://www.tandfonline.com/doi/full/10.3109/08958378.2010.489074.

27. Kelly FJ, Fussell JC. Air pollution and public health: emerging hazards and improved understanding of risk. Environ Geochem Health [Internet]. 2015 Aug 4 [cited 2018 Sep 19]; 37(4):631–49. Available from: http://link.springer.com/10.1007/s10653-015-9720-1.

28. Bezemer GFG. Particle deposition and clearance from the respiratory tract. 2009 Sep 17 [cited 2018 Sep 19]; Available from: https://dspace.library.uu.nl/handle/1874/35718.

29. Pope III A, Ezzati M, Dockery D. Fine-Particulate air pollution and life expectancy in the United States. 2009 [cited 2018 Sep 19]; Available from: https://www.northeastdiesel.org/pdf/Pope-PM-life-expectancy-NewEngJMed2009.pdf.

30. Di Q, Wang Y, Zanobetti A, Wang Y, Koutrakis P, Choirat C, et al. Air Pollution and Mortality in the Medicare Population. N Engl J Med [Internet]. 2017 Jun 29 [cited 2018 Sep 19];376(26):2513–22. Available from: http://www.nejm.org/doi/10.1056/NEJMoa1702747.

31. Valavanidis A, Fiotakis K, Vlachogianni T. Airborne Particulate Matter and Human Health: Toxicological Assessment and Importance of Size and Composition of Particles for Oxidative Damage and Carcinogenic Mechanisms. J Environ Sci Heal Part C [Internet]. 2008 Dec 2 [cited 2018 Sep 19];26(4):339–362. Available from: http://www.tandfonline.com/doi/abs/

10.1080/10590500802494538.

32. Mills NL, Donaldson K, Hadoke PW, Boon NA, MacNee W, Cassee FR, et al. Adverse cardiovascular effects of air pollution. Nat Clin Pract Cardiovasc Med [Internet]. 2009 Jan 25 [cited 2018 Sep 8];6(1):36–44. Available from: http://www.ncbi.nlm.nih.gov/pubmed/19029991.

33. Calderón-Garcidueñas L, Mora-Tiscareño A, Ontiveros E, Gómez-Garza G, Barragán-Mejía G, Broadway J, et al. Air pollution, cognitive deficits and brain abnormalities: A pilot study with children and dogs. Brain Cogn [Internet]. 2008 Nov [cited 2018 Sep 19];68(2):117–127. Available from: http://linkinghub.elsevier.com/retrieve/pii/S0278262608001747.

34. Genc S, Zadeoglulari Z, Fuss SH, Genc K. The Adverse Effects of Air Pollution on the Nervous System. J Toxicol [Internet]. 2012 [cited 2018 Sep 19];2012:1–23. Available from: http://www.ncbi.nlm.nih.gov/pubmed/22523490.

35. Illum L. Is nose-to-brain transport of drugs in man a reality? J Pharm Pharmacol [Internet]. 2004 Jan [cited 2018 Sep 19];56(1):3–17. Available from: http://doi.wiley.com/10.1211/0022357022539.

36. Gackière F, Saliba L, Baude A, Bosler O, Strube C. Ozone inhalation activates stress-responsive regions of the CNS. J Neurochem [Internet]. 2011 Jun 1 [cited 2018 Sep 19]; 117(6):961–72. Available from: http://doi.wiley.com/10.1111/j.1471-4159.2011.07267.x.

37. Sankowski R, Mader S, ValdÃ©s-Ferrer SI. Systemic Inflammation and the Brain: Novel Roles of Genetic, Molecular, and Environmental Cues as Drivers of Neurodegeneration. Front Cell Neurosci [Internet]. 2015 Feb 2 [cited 2018 Sep 19];9:28. Available from: http://www.ncbi.nlm.nih.gov/pubmed/25698933.

38. Teeling JL, Perry VH. Systemic infection and inflammation in acute CNS injury and chronic neurodegeneration: Underlying mechanisms. Neuroscience [Internet]. 2009 Feb 6 [cited 2018

Sep 19];158(3):1062–1073. Available from: http://www.ncbi.nlm.nih.gov/pubmed/18706982.

39. Qin L, Wu X, Block ML, Liu Y, Breese GR, Hong J-S, et al. Systemic LPS causes chronic neuroinflammation and progressive neurodegeneration. Glia [Internet]. 2007 Apr 1 [cited 2018 Sep 19];55(5):453–462. Available from: http://www.ncbi.nlm.nih.gov/pubmed/17203472.

40. Dallas S, Miller DS, Bendayan R. Multidrug Resistance-Associated Proteins: Expression and Function in the Central Nervous System. Pharmacol Rev [Internet]. 2006 Jun 1 [cited 2018 Sep 19];58(2):140–161. Available from: http://www.ncbi.nlm.nih.gov/pubmed/16714484.

41. Miller DS, Bauer B, Hartz AMS. Modulation of P-Glycoprotein at the Blood-Brain Barrier: Opportunities to Improve Central Nervous System Pharmacotherapy. Pharmacol Rev [Internet]. 2008 May 15 [cited 2018 Sep 19];60(2):196–209. Available from: http://www.ncbi.nlm.nih.gov/pubmed/18560012.

42. Chen X, Gawryluk JW, Wagener JF, Ghribi O, Geiger JD. Caffeine blocks disruption of blood brain barrier in a rabbit model of Alzheimer's disease. J Neuroinflammation [Internet]. 2008 Apr 3 [cited 2018 Sep 19];5(1):12. Available from: http://www.ncbi.nlm.nih.gov/pubmed/18387175.

43. Calderón-Garcidueñas L, Azzarelli B, Acuna H, Garcia R, Gambling TM, Osnaya N, et al. Air Pollution and Brain Damage. Toxicol Pathol [Internet]. 2002 Apr 2 [cited 2018 Sep 19];30(3):373–389. Available from: http://www.ncbi.nlm.nih.gov/pubmed/12051555.

44. Lewis TC, Robins TG, Dvonch JT, Keeler GJ, Yip FY, Mentz GB, et al. Air pollution-associated changes in lung function among asthmatic children in Detroit. Environ Health Perspect [Internet]. 2005 Aug [cited 2018 Sep 20];113(8):1068–1075. Available from: http://www.ncbi.nlm.nih.gov/pubmed/16079081.

45. WHO. WHO Air quality guidelines for particulate matter, ozone, nitrogen dioxide and sulfur

dioxide [Internet]. 2006 [cited 2018 Sep 19]. Available from: http://apps.who.int/iris/bitstream/handle/10665/69477/WHO_SDE_PHE_OEH_06.02_eng.pdf;jsessionid=CD198B0F1468BE9BEBFCFC18E71D4EA6?sequence=1.

46. Koenig P. BRICS – Potential and Future in an Emerging New World Economy - Global ResearchGlobal Research - Centre for Research on Globalization [Internet]. 2017 [cited 2018 Sep 19]. Available from: https://www.globalresearch.ca/brics-potential-and-future-in-an-emerging-new-world-economy/5609999.

47. Wu T. China, BRICs & the Environment | The Diplomat [Internet]. 2011 [cited 2018 Sep 19]. Available from: https://thediplomat.com/2011/11/china-brics-and-the-environment/.

48. Calderón-Garcidueñas L, Villarreal-Ríos R. Living close to heavy traffic roads, air pollution, and dementia. Lancet (London, England) [Internet]. 2017 Feb 18 [cited 2018 Sep 8]; 389(10070):675–677. Available from: http://www.ncbi.nlm.nih.gov/pubmed/28063596.

49. Andersson J, Oudin A, Sundström A, Forsberg B, Adolfsson R, Nordin M. Road traffic noise, air pollution, and risk of dementia – results from the Betula project. Environ Res [Internet]. 2018 Oct 1 [cited 2018 Sep 8];166:334–9. Available from: https://www.sciencedirect.com/science/article/pii/S0013935118303104?via%3Dihub.

50. Knapton S. Living near a busy road may raise risk of dementia, major study into pollution finds [Internet]. 2017 [cited 2018 Sep 19]. Available from: https://www.telegraph.co.uk/science/2017/01/04/living-near-busy-road-may-raise-risk-dementia-major-study-pollution/.

51. Block ML, Elder A, Auten RL, Bilbo SD, Chen H, Chen J-C, et al. The outdoor air pollution and brain health workshop. Neurotoxicology [Internet]. 2012 Oct [cited 2018 Sep 19];33(5): 972–84. Available from: http://linkinghub.elsevier.com/retrieve/pii/S0161813X12002100.

52. Fine Particulate Matter (PM2.5) in the United Kingdom [Internet]. 2012 [cited 2018 Sep 18].

Available from: http://www.defra.gov.uk/environment/quality/air/.

53. Date W. London targets WHO air quality limits by 2030 [Internet]. 2017 [cited 2018 Sep 8]. Available from: https://www.airqualitynews.com/2017/08/11/london-targets-air-quality-limits-2030/.

54. Sauer A. Why Is Alzheimer's More Likely in Women? [Internet]. 2018 [cited 2018 Sep 8]. Available from: https://www.alzheimers.net/8-12-15-why-is-alzheimers-more-likely-in-women/.

55. EPA. Air Quality Criteria for Ozone and Related Photochemical Oxidants. Mol Cell Biochem [Internet]. 2006;9(3):131–133. Available from: http://www.ncbi.nlm.nih.gov/pubmed/610.

56. Kheirbek I, Wheeler K, Walters S, Pezeshki G, Kass D, Advisor S, et al. Air Pollution and the Health of New Yorkers: The Impact of Fine Particles and Ozone [Internet]. [cited 2018 Sep 8]. Available from: https://www1.nyc.gov/assets/doh/downloads/pdf/eode/eode-air-quality-impact.pdf.

57. Moolgavkar SH. Air pollution and hospital admissions for chronic obstructive pulmonary disease in three metropolitan areas in the United States. Inhal Toxicol [Internet]. 2000 [cited 2018 Sep 8];12 Suppl 4:75–90. Available from: http://www.ncbi.nlm.nih.gov/pubmed/12881887.

58. NYC Gov Health. Chapter 16: Air Quality [Internet]. 2018 [cited 2018 Sep 8]. Available from: https://www1.nyc.gov/assets/planning/download/pdf/applicants/env-review/53_west_53/16_feis.pdf.

59. 40 C.F.R. § 50. Subchapter C - Air Programs - Part 50 - National Primary and Secondary Ambient Air Quality Standards. 2015; Available from: https://www.gpo.gov/fdsys/pkg/CFR-2015-title40-vol2/pdf/CFR-2015-title40-vol2-part50.pdf.

60. WHO. WHO | Ambient air pollution: A global assessment of exposure and burden of disease.

WHO [Internet]. 2016 [cited 2018 Sep 19]; Available from: http://www.who.int/phe/publications/air-pollution-global-assessment/en/.

61. Larsen B. SPEAKER Bjorn Larsen Summary: White Paper Report by Bjorn Larsen [Internet]. 2015 [cited 2018 Sep 9]. Available from: https://www.copenhagenconsensus.com/sites/default/files/brazil_air_pollution_resources.pdf.

62. Brauer M. PM2.5 air pollution, population exposed to levels exceeding WHO guideline value. 2015.

63. Berrueta V, Edward R, Masera O. Brazil Perspectives: Air Pollution | Copenhagen Consensus Center [Internet]. 2008 [cited 2018 Sep 19]. Available from: https://www.copenhagenconsensus.com/publication/brazil-perspectives-air-pollution.

64. Nandil J. PM2.5 levels this week were worse than Diwali 2014 [Internet]. 2014 [cited 2018 Sep 19]. Available from: https://toibnews.timesofindia.indiatimes.com/fivex.htm?errurl=timesofindia.indiatimes.com/india/PM2-5-levels-this-week-were-worse-than-Diwali/articleshow/45651422.cms.

65. TNN. '70% cut in PM 2.5 levels needed' | Delhi News - Times of India [Internet]. 2017 [cited 2018 Sep 19]. Available from: https://timesofindia.indiatimes.com/city/delhi/70-cut-in-pm2-5-levels-needed/articleshow/57381301.cms.

66. Chun Z. Can China meet its 2017 air quality goals? | Opinion | Eco-Business | Asia Pacific [Internet]. 2017 [cited 2018 Sep 19]. Available from: https://www.eco-business.com/opinion/can-china-meet-its-2017-air-quality-goals/.

67. Institute for Health Metrics and Evaluation. Russia - PM2.5 air pollution, population exposed to levels exceeding WHO guideline value (% of total) [Internet]. 2016 [cited 2018 Sep 9]. Available from: https://www.indexmundi.com/facts/russia/indicator/EN.ATM.PM25.MC.ZS.

68. European Environment Agency. Air quality in Europe — 2016 report — European

Environment Agency [Internet]. 2016 [cited 2018 Sep 19]. Available from: https://www.eea.europa.eu/publications/air-quality-in-europe-2016.

69. AQICN. London Air Pollution: Real-time PM2.5 Air Quality Index (AQI) [Internet]. 2018 [cited 2018 Sep 9]. Available from: https://aqicn.org/city/london/.

70. Greater London Authority. London Environment Strategy [Internet]. London; 2017 [cited 2018 Sep 9]. Available from: www.london.gov.uk.

71. Omoju O. Environmental Pollution is Inevitable in Developing Countries «Breaking Energy - Energy industry news, analysis, and commentary [Internet]. 2014 [cited 2018 Sep 9]. Available from: https://breakingenergy.com/2014/09/23/environmental-pollution-is-inevitable-in-developing-countries/.

72. United Nations Development Programme. Human Development Reports [Internet]. 2016 [cited 2018 Sep 9]. Available from: http://hdr.undp.org/en/composite/HDI.

73. The World Bank. PM2.5 air pollution, population exposed to levels exceeding WHO guideline value (% of total) | Data [Internet]. 2016 [cited 2018 Sep 9]. Available from: https://data.worldbank.org/indicator/EN.ATM.PM25.MC.ZS.

74. Martin Prince A, Wimo A, Guerchet M, Gemma-Claire Ali M, Wu Y-T, Prina M, et al. World Alzheimer Report 2015 The Global Impact of Dementia An AnAlysIs of prevAlence, IncIDence, cosT AnD TrenDs [Internet]. 2015 [cited 2018 Sep 9]. Available from: www.daviddesigns.co.uk.

75. Alzheimer's Disease International. Dementia statistics | Alzheimer's Disease International [Internet]. 2016 [cited 2018 Sep 9]. Available from: https://www.alz.co.uk/research/statistics.

76. Hendrie HC, Ogunniyi A, Hall KS, Baiyewu O, Unverzagt FW, Gureje O, et al. Incidence of dementia and Alzheimer disease in 2 communities: Yoruba residing in Ibadan, Nigeria, and African Americans residing in Indianapolis, Indiana. JAMA [Internet]. 2001 Feb 14 [cited

2018 Sep 9];285(6):739–747. Available from: http://www.ncbi.nlm.nih.gov/pubmed/11176911.

77. Chandra V, Pandav R, Dodge HH, Johnston JM, Belle SH, DeKosky ST, et al. Incidence of Alzheimer's disease in a rural community in India: the Indo-US study. Neurology [Internet]. 2001 Sep 25 [cited 2018 Sep 9];57(6):985–989. Available from: http:/www.ncbi.nlm.nih.gov/pubmed/11571321.

78. Li G, Shen YC, Chen CH, Zhau YW, Li SR, Lu M. A three-year follow-up study of age-related dementia in an urban area of Beijing. Acta Psychiatr Scand [Internet]. 1991 Feb [cited 2018 Sep 9];83(2):99–104. Available from: http://www.ncbi.nlm.nih.gov/pubmed/2017918.

79. Prince M, Acosta D, Ferri CP, Guerra M, Huang Y, Rodriguez JJL, et al. Dementia incidence and mortality in middle-income countries, and associations with indicators of cognitive reserve: a 10/66 Dementia Research Group population-based cohort study. Lancet [Internet]. 2012 Jul 7 [cited 2018 Sep 9];380(9836):50–8. Available from: http://www.ncbi.nlm.nih.gov/pubmed/22626851.

80. Murray AD, Staff RT, McNeil CJ, Salarirad S, Ahearn TS, Mustafa N, et al. The balance between cognitive reserve and brain imaging biomarkers of cerebrovascular and Alzheimer's diseases. Brain [Internet]. 2011 Dec 1 [cited 2018 Sep 9];134(12):3687–96. Available from: http://www.ncbi.nlm.nih.gov/pubmed/22102649.

81. NHS. Education may help reduce the risk of Alzheimer's disease - NHS [Internet]. 2017 [cited 2018 Sep 9]. Available from: https://www.nhs.uk/news/neurology/education-may-help-reduce-risk-alzheimers-disease/.

82. Morgan PL, Farkas G, Hillemeier MM, Maczuga S. Risk Factors for Learning-Related Behavior Problems at 24 Months of Age: Population-Based Estimates. J Abnorm Child Psychol [Internet]. 2009 Apr 5 [cited 2018 Sep 10];37(3):401–413. Available from: http://

www.ncbi.nlm.nih.gov/pubmed/19057886.

83. American Academy of Neurology. Low education level linked to Alzheimer's study shows [Internet]. Neurology. 2007 [cited 2018 Sep 9]. Available from: https://www.aan.com/.

84. Liu HC, Fuh JL, Wang SJ, Liu CY, Larson EB, Lin KN, et al. Prevalence and subtypes of dementia in a rural Chinese population. Alzheimer Dis Assoc Disord [Internet]. 1998 Sep [cited 2018 Sep 9];12(3):127–134. Available from: http://www.ncbi.nlm.nih.gov/pubmed/9772013.

85. Alzheimer's Society. How do drugs for Alzheimer's disease work? | Alzheimer's Society [Internet]. 2017 [cited 2018 Sep 19]. Available from: https://www.alzheimers.org.uk/about-dementia/treatments/drugs/how-do-drugs-alzheimers-disease-work.

86. Sheldrick G. Dementia cure at last: First drug to stop disease in its tracks | Express.co.uk [Internet]. 2016 [cited 2018 Sep 19]. Available from: https://www.express.co.uk/life-style/health/665115/Alzheimer-dementia-cure-drug-stop-disease.

87. Bellingham SA, Guo BB, Coleman BM, Hill AF. Exosomes: Vehicles for the transfer of toxic proteins associated with neurodegenerative diseases? Front Physiol. 2012;3 MAY(May).

88. Beseničar M, Maček P, Lakey JH, Anderluh G. Surface plasmon resonance in protein–membrane interactions. Chem Phys Lipids [Internet]. 2006 Jun 1 [cited 2018 Jul 25];141(1–2):169–178. Available from: https://www.sciencedirect.com/science/article/pii/S0009308406000326.

89. Suutari T. SURFACE PLASMON RESONANCE IN LIVING CELL SENSING − SPR Responses in Cell-Exosome Interactions Surface Plasmon Resonance in Living Cell Sensing -SPR Responses in Cell-Exosome Interactions. 2014 [cited 2018 Jun 1]; Available from: https://helda.helsinki.fi/bitstream/handle/10138/135725/Suutari - Master of the Universe.pdf?sequence=1.

90. Alzheimer's Research. New study shows funding for dementia research still too low | Alzheimer's Research UK [Internet]. 2015 [cited 2018 Sep 19]. Available from: https://www.alzheimersresearchuk.org/new-study-shows-funding-for-dementia-research-still-too-low/.

91. Wegerer J. Alzheimer's Research Spending vs. Annual Care Costs [Internet]. 2013 [cited 2018 Sep 19]. Available from: https://www.alzheimers.net/research-spending-vs-annual-care-costs/

92. Movement I. Sixth Leading Cause of Death [Internet]. [cited 2018 Sep 19]. Available from: http://act.alz.org/site/DocServer/2012_6th_Cause_Fact_Sheet.pdf?docID=7149.

93. Finch C, Chen J-C. Air Pollution exposures may increase risk of dementia. 2017.

94. Owenscooper. Is the Balearic Eco Tax already having a negative impact? | Owens Cooper Consulting [Internet]. 2016 [cited 2018 Sep 19]. Available from: http://owenscooper.co.uk/is-the-balearic-eco-tax-already-having-a-negative-impact/.

95. Rosenstein B. Environmental rollback will be costly [Internet]. 2017 [cited 2017 Mar 8]. Available from: http://www.baltimoresun.com/news/opinion/readersrespond/bs-ed-environment-letter-20170206-story.html.

96. Niño-Zarazúa M. UNU-WIDER: Blog: Three types of interventions that can improve the quality of education in developing countries [Internet]. 2016 [cited 2018 Sep 9]. Available from: https://www.wider.unu.edu/publication/three-types-interventions-can-improve-quality-education-developing-countries.

97. Burns A, Lustman F, Meerveld J. IMPROVING DEMENTIA CARE WORLDWIDE IDEAs AND ADVICE ON DEVELOPING AND IMPLEMENTING A NATIONAL DEMENTIA PLAN [Internet]. 2013 [cited 2018 Sep 9]. Available from: https://www.alz.co.uk/sites/default/files/pdfs/global-dementia-plan-report-ENGLISH.pdf.

98. Paddick S-M, Longdon A, Gray WK, Dotchin C, Kisoli A, Chaote P, et al. The association between educational level and dementia in rural Tanzania. Dement Neuropsychol [Internet]. 2014 [cited 2018 Sep 9];8(2):117–125. Available from: http://www.ncbi.nlm.nih.gov/pubmed/29213892.