The Role of Air Pollution Exposure in Multiple Sclerosis Development and Progression: The Saudi Arabian Context

by

Maha Alhazmi

BHS Epidemiology, Princess Nourah bint Abdulrahman University, 2017

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The Role of Air Pollution Exposure in Multiple Sclerosis Development and Progression: The Saudi Arabian Context

Maha Alhazmi, MPH
University of Pittsburgh, 2023

Abstract

The incidence of autoimmune diseases has been steadily rising in industrialized communities over the last few decades, and studies have shown that exposure to urban air pollution can increase the occurrence and severity of autoimmune diseases. The global prevalence of multiple sclerosis (MS), an autoimmune, inflammatory disease of the central nervous system, has increased from approximately 2.3 million to 2.8 million cases from 2013 to 2020. The disease etiology remains unclear, but evidence has shown that in addition to genetic predisposition, smoking, low vitamin D levels, and previous viral infection such as Epstein Barr Virus (EBV) can play a role in disease development and cause a higher relapse rate. The effects of air pollution on MS development and progression have been studied in recent years in a few countries, some of which have good to moderate levels of air pollution. However, the role of air pollution in the pathogenesis of MS, especially in countries that struggle with high levels of air pollution, is still unknown and needs to be elucidated. This essay focuses on the Kingdom of Saudi Arabia (KSA) as one of the countries that experience elevated air pollution levels and have witnessed a significant increase in MS prevalence. Its purpose is to present recent literature on the association between air pollution and the incidence and progression of MS as well as the latest data on MS prevalence and levels of air pollution and their main sources in KSA.
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1.0 Introduction

Air pollution is a public health issue of global importance that has been associated with increased morbidity and mortality. The incidence of autoimmune diseases has been steadily rising in industrialized communities over the last few decades, and population-based studies have shown that exposure to urban air pollution can increase the occurrence and severity of autoimmune diseases (Gawda et al., 2017; Zhao et al., 2019; Glencross et al., 2020; Adami et al., 2022; Izic et al., 2022). Air pollutant exposure has also been suggested to have detrimental effects on the central nervous system (CNS), such as neuroinflammation and neurodegeneration (Serafini et al., 2022). Recently, a few studies investigated the effects of air pollution on multiple sclerosis (MS) and proposed a possible risk, especially regarding disease exacerbation (Noorimotlagh et al., 2021). These findings highlight the need for more research to understand the role of air pollution in the pathogenesis of MS, especially in countries that struggle with high levels of air pollution. The Kingdom of Saudi Arabia (KSA) is one of the countries that experience elevated air pollution levels, especially in major cities. According to the World Health Organization’s (WHO) guidelines, the air quality in KSA is considered unhealthy as the annual average concentration of particulate matter 2.5 (PM2.5) reaches 88 µg/m³ and higher, exceeding the recommended maximum of 5 – 10 µg/m³. Other air pollutants are also of great concern, such as particulate matter 10 (PM10) and nitrogen dioxide (NO₂) (Health Effects Institute, 2019). The Kingdom has also witnessed a significant increase in MS prevalence, an estimated 41 cases per 100,000 total population (AlJumah et al., 2020a; Walton et al., 2020), which raises the question of whether any environmental exposures are contributing to the increasing number of MS cases. However, the effects of air pollution on MS development and progression in this region with poor air quality are
unknown. Therefore, this essay aims to present recent literature on the association between air pollution and the incidence and severity of MS as well as the latest data on MS prevalence and levels of air pollution and their primary sources in KSA.

More specifically, in relation to public health, this essay highlights the importance of future epidemiologic and mechanistic studies to assist in policy formulation to reduce sources of air pollution, improve air quality, preserve immune health, and reduce the risk of developing and exacerbating MS and other autoimmune diseases.
2.0 Review

This section describes MS, the epidemiology of MS, air pollution, and potential molecular mechanisms by which air pollution influences MS onset and progression.

2.1 Multiple sclerosis

MS is an autoimmune neurodegenerative disease of the CNS that is triggered by autoreactive CD4+ helper T (Th) cells, causing chronic inflammation, demyelination, and axon and neuronal loss. In MS, the immune system mistakenly attacks the CNS, particularly the myelin sheath, which is a layer of lipid and protein that protects the axons in the brain and spinal cord. This attack damages the myelin and strips it off the axons, leaving scars known as lesions or plaques (Fig. 1). The myelin sheath around axons is crucial for the transmission of electrical messages between regions within the CNS. A destroyed myelin sheath leaves the axons exposed to even further damage, leading to axon and neuronal loss, which is the main cause of irreversible and progressive neurologic decline in MS patients. MS is not considered fatal; however, disease complications can lead to premature death, especially in untreated or insufficiently treated MS. Research shows that patients with MS have a life expectancy of 7 to 14 years less than the general population (Scalfari et al., 2013). Some of the neurological signs or symptoms that MS patients can develop are numbness, muscle spasms, mobility problems, ataxia, visual or bladder problems, fatigue, depression, and MS-related cognitive impairment. As a multifactorial disease, the etiology of MS is complex and remains unclear, but a combination of genetics and environmental
influences, such as smoking, vitamin D deficiency, and viral infections like that of Epstein–Barr virus (EBV), have been reported to play a role in the development of the disease (Goldenberg et al., 2012; Huang et al., 2017; Pegoretti et al., 2020).

**Figure 1 Normal myelinated axon vs. demyelinated axon in MS.**


There are several different forms of MS. Relapsing-remitting MS (RRMS), the most common form of MS, mainly characterized by peripheral and central inflammation that leads to axonal damage and neuronal loss. RRMS is also characterized by clearly defined attacks (relapses) followed by periods of remission during which symptoms resolve spontaneously. After accumulating tissue damage over several years, RRMS can evolve into a secondary progressive form of MS (SPMS), in which neurologic function worsens gradually over time. Primary progressive MS (PPMS) is another form of MS in which 10% to 15% of patients develop directly
without experiencing clinical relapses (Koch et al., 2009; Goldenberg et al., 2012; Pegoretti et al., 2020; Cree et al., 2021; Bruce et al., 2021). There is also clinically isolated syndrome (CIS) and radiologically isolated syndrome (RIS), both of which are early signs of MS that may or may not progress to full-blown MS. CIS is characterized by a single event of neurological symptoms, while RIS does not show MS symptoms but has MS-like brain damage (Thompson et al., 2018).

2.1.1 Epidemiology of multiple sclerosis

Around 2.8 million people are living with MS worldwide according to the Atlas of MS, a global compendium of the epidemiology of MS (Fig. 2) (Walton et al., 2020). MS usually affects people during their peak productive ages of 20 to 40 years, making it one of the most common disabling neurological diseases among young adults. MS is more prevalent among women than men, with a female-to-male ratio as high as 3:1 (Walton et al., 2020). The incidence of MS varies by geographical location, ethnicity, and environmental influences. MS was found to be more prevalent among white people and in areas farthest from the equator (i.e., North America and Northern Europe) where there is less sunlight; however, several MS clusters have been found not to follow this trend (Turabelidze et al., 2008).
The higher incidence of MS in countries at higher latitudes is thought to be related to the lower levels of ultraviolet B (UVB) radiation, which is necessary to produce vitamin D in the skin in these regions (National MS Society, n.d.-a). Vitamin D plays a crucial role in regulating immunity as it can enhance innate immune responses and modulate and regulate the differentiation and activation of adaptive immunity, such as T and B cells. Vitamin D also has anti-inflammatory effects that help reduce excessive inflammation that can damage body tissues. Vitamin D insufficiency has been linked to an increased risk of autoimmune disorders, including MS (Aranow et al., 2011; Szymczak et al., 2016; Dupuis et al., 2021). Studies have shown that people with MS tend to have lower levels of vitamin D compared to healthy individuals, suggesting that vitamin D insufficiency may be associated with an increased risk of developing MS and a more severe disease.
course. A worldwide cohort study found that living at higher latitudes is associated with earlier MS onset (Tao et al., 2016). Another cohort study conducted in Denmark showed that vitamin D supplementation reduces relapse rates in RRMS patients (Laursen et al., 2016).

Given the cruciality of vitamin D in immune modulation and the prevention of inflammation and autoimmunity, it is vital to shed light on air pollutants and their indirect contribution to vitamin D deficiency through the reduction of UVB intensity at the ground level, which has consequences for health. As sun exposure accounts for more than 90% of vitamin D production, this is especially concerning for countries with high levels of atmospheric pollutants. (Sections 2.3.1 and 3.2.4 further elaborate on this relationship and how it might adversely impact MS.)

2.2 Air pollution

2.2.1 Air pollution and disease burden

Air pollution is the single greatest environmental health risk, accounting for an estimated 7 million premature deaths each year and 3.2% of the global disease burden. It was the fifth-ranked risk factor for mortality in 2017. Recent data from the WHO suggest that more than 90% of the world’s population breathes polluted air that exceeds WHO guideline limits (WHO, 2022). Along with the accumulated literature linking air pollution to both respiratory and cardiovascular morbidity and mortality (Babatola et al., 2018), emerging evidence suggests an association between air pollution and autoimmune diseases and neurological disorders (Zhao et al., 2019; Health Effects Institute, 2019). This effect is especially due to ambient particulate matter (PM).
2.2.2 Components of modern-day atmospheric pollutants

Air pollution is a heterogeneous mixture of gaseous, liquid, and solid constituents resulting from the interactions of multiple emissions and chemical reactions, each of which has distinct chemical and physical properties that can impact biological systems. Air pollution mainly stems from anthropogenic activity, such as vehicle emissions, industrial processes, manufacturing, and power generation. Air pollutants include PM, a family of particles characterized by varying sizes (coarse particles PM$_{10}$, fine particles PM$_{2.5}$, very fine particles <PM$_{1}$), gases (i.e., nitrogen oxides [NOx], sulfur oxides [SO$_x$], ozone [O$_3$], and carbon monoxide [CO]), volatile organic compounds (VOCs), heavy metals, and polycyclic aromatic hydrocarbons (PAHs) (Hahad et al., 2020). Fine particle pollution (PM$_{2.5}$) is a major public health concern worldwide due to its potential systemic toxicity as smaller particles could penetrate deep into the lung and bloodstream (Xing et al., 2016). Additionally, a recent analysis showed that chronic exposure to PM$_{2.5}$ contributed to 4 million premature deaths in 2019 (Health Effects Institute, 2019); Lelieveld et al. published similar findings (Lelieveld et al., 2015). Table 1 shows the WHO air pollution guidelines that have recently been changed to save more lives, also known as “criteria” air pollutants as per the U.S. Environmental Protection Agency.

<table>
<thead>
<tr>
<th>Pollutant</th>
<th>WHO Guidelines 2005</th>
<th>WHO Guidelines 2021</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PM$_{10}$</strong></td>
<td>Annual</td>
<td>20 µg/m$^3$</td>
</tr>
<tr>
<td></td>
<td>24-hour</td>
<td>50 µg/m$^3$</td>
</tr>
<tr>
<td><strong>PM$_{2.5}$</strong></td>
<td>Annual</td>
<td>10 µg/m$^3$</td>
</tr>
</tbody>
</table>
### 2.3 Air pollution and multiple sclerosis

Mechanistic studies have demonstrated that air pollutants can disrupt the immune system at a molecular level. For example, PM has been shown to enhance the expression of several inflammatory pathways, produce pro-inflammatory cytokines, and upregulate the activation of genes involved in the inflammatory response. There is mounting concern that air pollution increases the incidence and severity of autoimmune diseases, and although the association between long-term exposure to air pollution and the risk of developing autoimmune diseases is still under study, evidence has shown that exposure to air pollution can influence autoimmunity by augmenting autoimmune responses and increasing systemic inflammation (Zhao et al., 2019;
Adami et al., 2022). Generally, the negative impacts of air pollution are believed to result mainly from the oxidative stress-inducing nuclear factor-κB (NF-κB) and mitogen-activated protein kinase (MAPK) pathways. Even inert particles can produce oxidative stress as they stimulate an inflammatory response. Studies have also shown that air pollutants can stimulate neurogenic inflammation (Baeza-Squiban et al., 1999; Reibman et al., 2002; Veronesi et al., 2001; Nel et al., 2001; Pourazar et al., 2005; Ritz., et al., 2010). In the case of MS, inflammation is a major pathological factor, and the associated oxidative stress contributes to tissue damage and enhances existing inflammatory responses (Pegoretti et al., 2020). Therefore, it is critical to understand and further explore the possible molecular mechanisms through which air pollution influences MS onset and disease severity.

### 2.3.1 Possible mechanisms by which air pollution exposure influences multiple sclerosis

While the role of air pollution in the pathogenesis of MS is not yet fully understood, exposure to atmospheric pollutants can stimulate a number of mechanisms that can influence MS incidence and progression. Human and animal studies have revealed four potential mechanisms by which air pollution may influence MS incidence and relapses (Fig. 3) (Karpus et al., 1997; Block et al., 2005; Kooij et al., 2010; Mousavi et al., 2017; Zhao et al., 2019; Glencross et al., 2020; Noorimotlagh et al., 2021):

1. The main potential mechanism involves dysimmune inflammatory responses following oxidative stress, which cause neuroinflammation and the breakdown of the normal immunity-tolerance balance, thereby compromising the blood-brain barrier and leading to neuroinflammation.
2. The second potential mechanism involves the olfactory system, where inhaled air particles that deposit in the nose can translocate and cross the blood-brain barrier, by which air pollutants can penetrate deep into the brain parenchyma.

3. The third potential mechanism involves the air pollution-mediated alteration of the epigenetics of neurogliocytes, which would result in the production of pro-inflammatory cytokines by innate and adaptive immune cells and autoimmunity in the cerebrum.

4. The fourth mechanism involves vitamin D deficiency as an indirect effect of air pollution exposure. Hypovitaminosis D is associated with a higher risk of developing MS, a higher relapse rate, and an increased number of MS lesions in the brain (Mowry et al., 2012). Air pollutants can absorb UVB radiation in the atmosphere, limiting the amount of UVB radiation reaching the ground level. This leads to a reduction in vitamin D synthesis in the skin and consequently increases the risk of MS relapse.
Figure 3 Potential mechanisms by which exposure to air pollution influences MS.
3.0 Analysis

This section presents recent studies on the association between exposure to air pollution and the onset and progression of MS, the prevalence of MS and the levels of air pollution in KSA.

3.1 Population-based studies of air pollution and multiple sclerosis

The role of air pollution in the risk of developing and exacerbating MS has gained more attention lately. A few studies have investigated this subject, reporting mixed results.

3.1.1 Particulate matter

An Italian study clinically investigated the effect of PM\textsubscript{10} on MS patients and healthy controls. The study suggests that exposure to PM\textsubscript{10} can increase disease activity in MS patients due to the upregulation of the expression of C-C chemokine receptor 6 (CCR6) on circulating CD4+ Th cells, which induces innate immune cells and the production of Th17 polarizing cytokines (Cortese et al., 2020). Th cells play central roles in the cell and tissue damage characteristic of many inflammatory and autoimmune diseases, such as MS (Yasuda et al., 2019). Another Italian ecological study explored the spatial distribution of MS cases and PM\textsubscript{2.5} concentrations. The study found a lower risk of MS among individuals living in rural areas with low concentrations of PM\textsubscript{2.5} (Bergamaschi et al., 2021). A third Italian study found that MS prevalence was significantly higher in urban areas than in isolated villages or rural areas in the
province of Padua. The authors also strongly associated PM$_{2.5}$ with MS prevalence, implying that air pollutants could be a potential environmental risk factor for MS (Tateo et al., 2019). Angelici et al. evaluated the association between PM$_{10}$ daily averages and MS hospital admission in Lombardy, Italy. The study found that an increased risk of MS hospitalization was associated with PM$_{10}$ exposure at different time intervals (0–28 days); exposure to PM$_{10}$ between days 0 and 7 had the maximum effect on MS hospitalization. At the highest quartile of the PM$_{10}$ concentration, hospital admission for MS increased by 42% (Angelici et al., 2016). Oikonen et al. found similar results: a four-fold increased risk of MS relapse on days when the levels of PM$_{10}$ were in the highest quartile. The authors of the two studies above speculated that the relationship between PM$_{10}$ exposure and high MS hospitalization could be due to the following mechanisms: 1) exposure to particulate air pollution could increase susceptibility to infections, thus triggering MS relapses and 2) inhaled air particles could influence autoimmunity by facilitating antigen presentation and augmenting autoimmune responses (Oikonen et al., 2003; Ritz et al., 2010). Similarly, Roax et al. reported a positive association between PM$_{10}$ exposure and the risk of MS relapse, implicating the oxidative stress mechanism as a potential cause (Roax et al., 2017). Others have also published similar findings (Bergamaschi et al., 2018; Gregory et al., 2008; Yuchi et al., 2020).

### 3.1.2 Mixture of pollutants

A French case-crossover study investigated the effect of short-term exposure to PM$_{10}$, NO$_2$, C$_6$H$_6$, O$_3$, and CO on MS relapse occurrence. The study shows that exposure to PM$_{10}$, NO$_2$, and O$_3$ was significantly associated with the risk of triggering MS relapses, attributed to the induction of neuroinflammation and oxidative cascade reactions (Jeanjean et al., 2018). A study was
conducted in Tehran, Iran, to evaluate the possible association between chronic exposure to air pollution and the distribution of prevalent MS cases. The MS cases showed a clustered pattern and were significantly correlated with the concentration of PM$_{10}$, SO$_2$, NO$_2$, and NOx (Heydarpour et al., 2014). Moreover, a Turkish study found that the prevalence of MS was more than double in an area home to an iron and steel factory compared to a rural city 40 km away (Börü et al., 2020). Börü et al. also found similar results in another population that lived near an iron and steel factory (Börü et al., 2018). Lavery et al. examined the association between the six “criteria” air pollutants and pediatric MS. PM$_{2.5}$, SO$_2$, CO, and lead air emissions were significantly associated with higher odds of pediatric MS compared with healthy controls. Further, the pediatric MS patients were found to live closer to Toxic Release Inventory (TRI) sites that released high levels of toxic chemicals than healthy controls (Lavery et al., 2018). However, some studies found different results—no association between air pollution and the risk of MS (Palacios et al., 2017; Carmona et al., 2018; Bai et al., 2018).

Taken together, these population-based studies suggest a potential role for air pollution in the pathogenesis of MS and in exacerbating disease progression by accelerating biological pathways. Many studies have observed an increased risk of MS relapse due to exposure to PM$_{10}$, suggesting that PM$_{10}$ could be a novel risk factor for MS. Experiencing frequent relapses and accumulated tissue damage would accelerate time to severe disability and cause more neurological damage. Therefore, it is of great importance to further research the mechanistic effects of air pollution on MS exacerbation and, thus, take steps toward air pollution mitigation and control measures.
3.2 Multiple sclerosis and air pollution in the Kingdom of Saudi Arabia

The effects of air pollution on MS development and exacerbation in KSA are unknown as research on this area is scarce. This section presents the latest data on the prevalence of MS in KSA, climate and precipitation, how these may influence air quality, and levels of air pollution in the region. In addition, given the crucial role of vitamin D in immunity and inflammation, section 3.2.4 briefly discusses vitamin D deficiency in the Kingdom in relation to air pollution and MS.

3.2.1 Multiple sclerosis in Saudi Arabia

It is difficult to provide an exact estimate of the prevalence of MS in KSA as few epidemiological hospital-based studies have been conducted. However, some estimates suggest that the prevalence of MS in KSA is between 30 and 40 cases per 100,000 people (Bohlega et al., 2013; Yamout et al., 2020). Although this is lower than the prevalence of MS in many western and neighboring countries (e.g., Qatar, Kuwait, and United Arab Emirates), this observation could be attributed to the lack of data, underreporting of cases, and an inadequate national registry as reported in several studies (Heydarpour et al., 2015; AlJumah et al., 2020a; AlJumah et al., 2020b). Fortunately, in 2015, the first nationwide multicenter MS registry was launched in the Kingdom, which led AlJumah et al. to report an estimated projected prevalence of MS for the whole population of 40.4 cases per 100,000 population and 61.95 cases per 100,000 Saudi nationals (Tables 2 and 3). Similarly, the Atlas of MS reported that the estimated prevalence of MS in KSA is 41 cases per 100,000 (Walton et al., 2020). These recent estimates on the increased prevalence of MS could relocate the Kingdom from a low to a moderate-to-high risk zone as per the Kurtzke classification (AlJumah et al., 2020a). AlJumah et al. have emphasized that the estimated number
of current and projected MS cases could be under or overestimated because not all hospitals in KSA are registered in the national MS registry yet (Appendix A). The Atlas of MS has also reported an increased prevalence of MS in the Middle East and North African region (MENA) (Walton et al., 2020; The Atlas of MS, 2022). Yamout et al. found that MS patients in the MENA region had an earlier age of onset and a more severe and disabling MS course compared with those in the West (Yamout et al., 2020). Therefore, it is important to investigate the possible environmental exposures influencing the disease phenotype in the region, including air pollution.

Table 2 MS Prevalence in Saudi Arabia.

From “Rising prevalence of multiple sclerosis in Saudi Arabia, a descriptive study” by AlJumah, et al., 2020a, *BMC neurology*, 20(1), 49. ([https://doi.org/10.1186/s12883-020-1629-3](https://doi.org/10.1186/s12883-020-1629-3)). Reprinted with permission under the terms of the Creative Commons Attribution 4.0 International License ([http://creativecommons.org/licenses/by/4.0/](http://creativecommons.org/licenses/by/4.0/)).

<table>
<thead>
<tr>
<th>Regions</th>
<th>Total hospital (MS)</th>
<th>Hospitals Included in Registry</th>
<th>MS patients from 20 hospital</th>
<th>Prevalence/100000 population</th>
<th>Projected prevalence/100000 population</th>
</tr>
</thead>
<tbody>
<tr>
<td>Western Region</td>
<td>30</td>
<td>7</td>
<td>990</td>
<td>9.3</td>
<td>39.9</td>
</tr>
<tr>
<td>Central Region</td>
<td>36</td>
<td>7</td>
<td>966</td>
<td>9.0</td>
<td>46.3</td>
</tr>
<tr>
<td>Eastern Region</td>
<td>22</td>
<td>4</td>
<td>378</td>
<td>7.7</td>
<td>42.4</td>
</tr>
<tr>
<td>Southern Region</td>
<td>9</td>
<td>2</td>
<td>173</td>
<td>3.6</td>
<td>16.2</td>
</tr>
<tr>
<td>Northern Region*</td>
<td>8</td>
<td>0</td>
<td>109</td>
<td>4.4</td>
<td>35.2</td>
</tr>
<tr>
<td>Total “2017”</td>
<td>105</td>
<td>20</td>
<td>2516</td>
<td>7.7</td>
<td>40.4</td>
</tr>
</tbody>
</table>

*Patients referred to other regions. For calculating projected prevalence for northern region we assumed 109 patients were referred from a single hospital of northern region to hospitals in other regions.
Table 3 Prevalence of MS among Saudi Nationals.

From “Rising prevalence of multiple sclerosis in Saudi Arabia, a descriptive study” by AlJumah, et al., 2020a, *BMC neurology*, 20(1), 49. (https://doi.org/10.1186/s12883-020-1629-3). Reprinted with permission under the terms of the Creative Commons Attribution 4.0 International License (http://creativecommons.org/licenses/by/4.0/).

<table>
<thead>
<tr>
<th>Regions</th>
<th>Saudis nationals</th>
<th>MS patients from 20 hospital (Saudi Nationals)</th>
<th>Prevalence/ 100,000 population</th>
<th>Projected prevalence/100,000 population</th>
</tr>
</thead>
<tbody>
<tr>
<td>Western Region</td>
<td>5,892,821</td>
<td>931</td>
<td>15.8</td>
<td>67.7</td>
</tr>
<tr>
<td>Central Region</td>
<td>5,667,865</td>
<td>833</td>
<td>14.7</td>
<td>75.6</td>
</tr>
<tr>
<td>Eastern Region</td>
<td>5,892,821</td>
<td>371</td>
<td>7.6</td>
<td>64.9</td>
</tr>
<tr>
<td>Southern Region</td>
<td>3,777,879</td>
<td>173</td>
<td>3.6</td>
<td>20.7</td>
</tr>
<tr>
<td>Northern Region*</td>
<td>1,929,435</td>
<td>107</td>
<td>5.5</td>
<td>44.0</td>
</tr>
<tr>
<td>Total “2017”</td>
<td>20,408,362</td>
<td>2415</td>
<td>11.8</td>
<td>61.95</td>
</tr>
</tbody>
</table>

* Patients in the northern region were referred to facilities in other regions. For calculating projected prevalence for northern region we assumed 107 Saudi patients were referred from a single hospital of the northern region to hospitals in other regions.

3.2.2 Climate and precipitation in Saudi Arabia

Some atmospheric conditions affect air quality, such as temperature, wind, humidity, precipitation, and air pressure. Therefore, the weather is a strong determinant of air pollution. Some pollutants, such as ground-level ozone (O₃), are worse in the summer heat, while others are worse in winter. High vegetation density, which many regions in Saudi lack, also has a positive effect on air quality (i.e., reducing particulate pollution) (Nowak et al., 2014; UCAR, n.d.). Therefore, it is relevant to briefly describe the climate characteristics of KSA. Except for the southwestern part of the country, Saudi Arabia is characterized by a desert climate. The central region experiences extremely hot and dry summers, with temperatures averaging 27 °C to 43 °C inland and 27 °C to 38 °C in coastal areas. In winter, the temperatures range from 8 °C to 20 °C in the central areas, with higher temperatures (19 °C–29 °C) recorded around the Red Sea’s coast. Except for the southwest, where rainfall typically ranges between 400 and 600 mm per year, most of the country experiences below 150 mm of annual rainfall. The annual average wind speed in
the majority of areas in Saudi ranges between 6.0 and 8.0 m/s (Metz et al., 1992; World Bank, n.d.-a).

### 3.2.3 Air pollution in Saudi Arabia

Along with the climate pattern in KSA, several other factors could have a detrimental effect on the air quality in the region; this includes the following: the Kingdom has an economy dominated by the oil-based industry, a heavy traffic load as the most common mode of transportation is cars, and frequent dusty days and sand and dust storms due to its arid nature (Radwan et al., 2022; Global EDGE, 2021; World Bank, n.d.-b). In addition, 83.33% of the Saudi population lives in urban areas (United Nations, 2023), which have worse air quality and higher levels of air pollution compared to rural regions (Kurt et al., 2016). Additionally, as a car-dependent country, traffic-related emissions play a critical role in contributing to the high levels of air pollution. Lelieveld et al. estimated that traffic emissions are responsible for approximately 5% of air PM$_{2.5}$-related mortality globally and up to 20% in Germany, the United Kingdom, and the United States (Lelieveld et al., 2015). Silva et al. also estimated that traffic emissions contributed to 20%–26% of the total ozone-related mortality in the Middle East (Silva et al., 2015).

In this essay, for accuracy, information on the concentration of air pollution in the KSA was acquired from published articles. KSA is one of the countries that struggle with high levels of air pollution; according to the State of Global Air 2020 report, Saudi Arabia’s annual mean of PM$_{2.5}$ is 62 µg/m$^3$, which is 12 times the WHO recommended value (5 µg/m$^3$). Figs. 4 and 5 show the global annual average PM$_{2.5}$ concentrations in 2017. In the MENA region, KSA had PM$_{2.5}$ concentrations of 88 µg/m$^3$, and similarly high levels were recorded in neighboring countries, including Qatar (91 µg/m$^3$), Bahrain (71 µg/m$^3$), Iraq (62 µg/m$^3$), and Kuwait (61 µg/m$^3$). Air
pollution is ranked among the top five risk factors for deaths in KSA, with air pollution being attributed to over 18,000 deaths in 2019 (Appendix B). According to the State of Global Air reports, exposure to ambient PM$_{2.5}$ has reduced life expectancy by an estimated average of 1 year and 3 months in the MENA region (Health Effects Institute, 2019) and 1 year and 9 months in KSA (Health Effects Institute, 2020). Studies have shown that chronic exposure to high average PM$_{2.5}$ concentrations is the most consistent predictor of mortality from respiratory, cardiovascular, and other types of diseases. It is also worth noting that dust coming from the Sahara Desert contributes to the high particulate concentrations in the region (Health Effects Institute, 2019). Dust particles, 1–8 µm in diameter, can travel large distances and can also carry toxins, metals, and microbes (Rice et al., 2017).

![Figure 4](soga_2019_report.pdf#stateofglobalair.org) Annual average PM2.5 concentrations in 2017 relative to the WHO Air Quality Guideline.

A recent study investigated the effects of PM$_{10}$, NO$_2$, and O$_3$, along with meteorological parameters, on the transmission of coronavirus disease 2019 (COVID-19) in three major cities in KSA (Riyadh, Jeddah, and Makkah). The PM$_{10}$ concentration exceeded the WHO-recommended average daily threshold of 45 μg/m$^3$ in the three cities (Ben Maatoug et al., 2021). Table 4 shows the daily average concentrations of the three air pollutants as measured by Ben Maatoug et al.
Table 4 Daily average concentrations of PM10, NO2, and O3 between March 9, 2020, and November 19, 2020, in the cities of Riyadh, Jeddah, and Makkah, Saudi Arabia.


<table>
<thead>
<tr>
<th>City</th>
<th>Pollutant</th>
<th>Mean</th>
<th>Std error</th>
<th>Minimum</th>
<th>Maximum</th>
<th>WHO Recommendation 24-hour (WHO, 2021)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Riyadh</td>
<td>PM10</td>
<td>351</td>
<td>14.98</td>
<td>310</td>
<td>418</td>
<td>45 μg/m³</td>
</tr>
<tr>
<td></td>
<td>NO2</td>
<td>38.5</td>
<td>10.55</td>
<td>23.4</td>
<td>53.1</td>
<td>25 μg/m³</td>
</tr>
<tr>
<td></td>
<td>O3</td>
<td>42.4</td>
<td>8.41</td>
<td>28.36</td>
<td>58.6</td>
<td>---</td>
</tr>
<tr>
<td>Jeddah</td>
<td>PM10</td>
<td>128</td>
<td>25.3</td>
<td>98.5</td>
<td>173.6</td>
<td>45 μg/m³</td>
</tr>
<tr>
<td></td>
<td>NO2</td>
<td>33.7</td>
<td>3.28</td>
<td>27.4</td>
<td>42.3</td>
<td>25 μg/m³</td>
</tr>
<tr>
<td></td>
<td>O3</td>
<td>52.12</td>
<td>4.31</td>
<td>43.61</td>
<td>63.47</td>
<td>---</td>
</tr>
<tr>
<td>Makkah</td>
<td>PM10</td>
<td>156.8</td>
<td>8.38</td>
<td>142.5</td>
<td>169.3</td>
<td>45 μg/m³</td>
</tr>
<tr>
<td></td>
<td>NO2</td>
<td>16.46</td>
<td>2.32</td>
<td>12.7</td>
<td>20.15</td>
<td>25 μg/m³</td>
</tr>
<tr>
<td></td>
<td>O3</td>
<td>42.8</td>
<td>7.6</td>
<td>34.21</td>
<td>51.62</td>
<td>---</td>
</tr>
</tbody>
</table>

Table 4 shows that between March and November 2020, the daily average concentration of PM10 in all three cities greatly exceeded the WHO-recommended average daily exposure. PM10 and NO2 daily concentrations were the highest in Riyadh city, where the highest MS prevalence is also found (i.e., the central region, including Riyadh city). This raises a question regarding the
possible health effects of these high levels of air contaminants on people with MS (i.e., increasing disease severity). In addition, Ben Maatoug et al. proposed that 1) air pollution can weaken the respiratory system, resulting in an increase in COVID-19 cases and more severe infection and 2) suspended particulates can play a role in spreading infectious diseases, such as severe acute respiratory syndrome and avian flu, as viruses can survive for several hours in air particles. Such effects must be considered because people with MS are at higher risk of infections due to disease-modifying therapies that suppress the immune system to reduce the risk of relapses. Infections can temporarily worsen MS symptoms, also called pseudo-relapse, or influence the risk of genuine relapse (Steelman et al., 2015; Lechner-Scott et al., 2020).

### 3.2.4 Air pollution, vitamin D deficiency and possible risk of multiple sclerosis

Given the large number of studies linking vitamin D deficiency to MS onset and higher relapse rates, investigating the indirect effects of air pollution on vitamin D deficiency and its subsequent effect on MS is critical. As described in sections 2.1.1 and 2.3.1, air pollution is one of the chief factors decreasing the intensity of UVB on the ground, with a subsequent reduction in the synthesis of vitamin D in the skin. Epidemiological studies from different geographic regions reported a high prevalence of vitamin D deficiency in populations that lived in highly polluted areas (Hosseinpanah et al., 2010; Feizabad et al., 2017; Agarwal et al., 2002; Manicourt et al., 2008; Calderón et al., 2015; Baïz et al., 2012). Kelishadi et al. reported a negative association between air quality index (AQI) and UVB radiation (Kelishadi et al., 2014).

Vitamin D deficiency is highly prevalent in the MENA region although it receives abundant sunshine throughout the year. KSA has a noticeably high prevalence of vitamin D deficiency across all demographics (63–81%) (Al-Daghri et al., 2018; Al-Alyani et al., 2018).
recent study in Kuwait, a neighboring country with a similar climate and air pollution levels, found that levels of air pollutants such as benzene, ethyl-benzene, NO, SO₂, O₃, and PM₁₀ were negatively associated with the UVB intensity at ground level. Such information raises questions about the potential association between air pollution, vitamin D deficiency, and MS in KSA, highlighting the importance of more research in this area.
4.0 Conclusion

MS is a multifactorial neurodegenerative disease of the CNS. Recent studies have implicated air pollution as a risk factor for MS onset and progression through the interaction of air pollutants with the body’s immune system. Some of the key immunological consequences of exposure to air pollution are the secretion of pro-inflammatory cytokines, T-cell imbalance, systematic inflammation, and vitamin D insufficiency, which contribute to the development and exacerbation of MS. Research on this area is scarce in KSA; therefore, conducting studies to describe and quantify the effects of air pollution on MS and other autoimmune diseases in the region should be a research priority.

Given the information presented in this essay regarding the effects of air pollution on the pathogenesis of MS, along with the absence of related studies in KSA, the following recommendations, which are divided into research-related and mitigation measures, should be considered:

1. Research-related:
   
   o Conduct ecological studies to provide preliminary results on the possible association between MS prevalence and exposure to air pollution.
   
   o Given that air quality significantly improved during the COVID-19 lockdown, investigate the impact of the COVID-19 lockdown in terms of air pollution on MS hospital admissions compared to other years.
   
   o Utilize a Geographic Information System (GIS) to visualize MS clustering, spatial patterns, and the distribution of risk factors across time (i.e., air pollution).
o Investigate the association of different pollutants with UVB intensity on the earth’s surface as well as the correlation between air pollution and the prevalence of vitamin D deficiency in different Saudi regions.

o Study the immunological mechanisms that underlie the clinical association between exposure to air pollution and inflammatory activity in MS patients. Additionally, study the pro-inflammatory effects of PM$_{10}$ exposure on MS patients given the frequency of dusty days in the region.

o Investigate the effects of dust storms on MS relapse rate.

2. Mitigation measures:

o Implement a massive governmental tree-planting effort to weaken the intensity of sand and dust storms that blow through inhabited areas (i.e., cities). Planting fences of native trees, so-called shelterbelts, around cities would provide considerable benefits in terms of reducing wind velocities, retaining soil moisture, providing food and cover for wildlife, and maintaining a fine appearance and a more livable environment. Such a strategy is shown to be highly effective in controlling blowing dust and soil erosion (Wei et al., 2020; Zon, 1935). This would also reduce the adverse health effects caused by sand and dust storms on people with asthma and respiratory diseases as well as other susceptible groups.

o Plant atmospheric-pollutant-tolerant trees that effectively reduce air pollution in heavily polluted areas. Alotaibi et al. suggested a particular tree species to grow specifically around pollution sources such as industries and vehicle emissions (i.e., roadsides) to enhance the air quality in the capital city Riyadh.
and other metropolitan areas in the Kingdom. Tree species showing a high air pollution tolerance index are *F. altissima*, followed by *Z. spina-christi* and *A. lebbeck* (Alotaibi et al., 2020).

- Increase the number of adequate air quality monitors across the Kingdom for research use, informing air quality policies, and keeping the public informed about the levels of air pollution in their region.

- Raise awareness among MS patients to stay indoors during dust storms, wear masks, or install air purifiers. Although there is little research on behavioral interventions to reduce exposure to indoor and outdoor air pollution, these measures would at least provide some protection (Rice et al., 2017).
Appendix A The number of hospitals participated in the MS registry, Saudi Arabia.¹

Appendix Figure 1.

¹ From “Rising prevalence of multiple sclerosis in Saudi Arabia, a descriptive study” by AJumah, et al., 2020a, BMC neurology, 20(1), 49. (https://doi.org/10.1186/s12883-020-1629-3). Reprinted with permission under the terms of the Creative Commons Attribution 4.0 International License (http://creativecommons.org/licenses/by/4.0/).
Appendix B Air pollution and health factsheet: Saudi Arabia

**Saudi Arabia**

**Air Pollution and Health Factsheet**

Air pollution was among the top 5 risk factors for death in Saudi Arabia in 2019, accounting for nearly 14% of all deaths (more than 18 thousand). Considered separately, ambient particulate matter (PM$_{2.5}$) ranked as the first leading risk factor for deaths, and household air pollution (HAP) ranked seventh. Ozone was not in the top 20 risk factors.

**Key statistics at a glance for 2019**

- 100% of the population of Saudi Arabia lives in areas where PM$_{2.5}$ levels are above the least stringent WHO Interim Target for healthy air (35 µg/m$^3$)
- 25% of outdoor PM$_{2.5}$ comes from fossil-fuel combustion (i.e., coal, oil and gas)
- 7% of deaths due to air pollution are in children under 5

**Exposure to Air Pollution**

- **PM$_{2.5}$** (presented as population-weighted annual average concentration)
  - Lower in 2019 (62 µg/m$^3$) than in 2010 (63 µg/m$^3$)
  - Higher than the global average (44 µg/m$^3$)
  - Saudi Arabia ranks third among 21 North Africa and Middle East countries
  - No documented stations monitored for PM$_{2.5}$ in Saudi Arabia ***

- **Ozone** (presented as population-weighted seasonal average concentration)
  - Higher in 2019 (58 ppb) than in 2010 (54 ppb)
  - Higher than the global average (50 ppb)

- **HAP** (% of population relying on solid fuels for cooking)
  - Lower in 2019 (1%) than in 2010 (2%)

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*Please note that PM$_{2.5}$ concentrations reported here are estimated using a combination of satellite data, ground air quality monitoring data, and chemical transport models. These estimates can be more uncertain where ground monitoring data are limited or not available. In Saudi Arabia, the best estimate of the annual average exposure is 62 µg/m$^3$, but it may range from 48 µg/m$^3$ to 79 µg/m$^3$. **Based on data from GBD-MAPS - Global Project. Find out more.***

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Appendix Figure 2.

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Health Impacts of Air Pollution

- Air pollution is among the top 5 risk factors for death in Saudi Arabia; more than 18 thousand in 2019 deaths were linked to air pollution.
- There are 112 deaths per 100,000 people due to air pollution in Saudi Arabia which is higher than the global average (86 deaths per 100,000), adjusted for differences in age.
- 7% of total air-pollution-attributable deaths in Saudi Arabia are in children under 5, and 15% are in adults over 70.
- Air pollution reduced life expectancy in Saudi Arabia by 1.9 years.

Percentage of Deaths (by Cause) Due to Air Pollution in Saudi Arabia in 2019

- Stroke: 35%
- Diabetes: 24%
- Ischemic heart disease: 33%
- COPD: 43%
- Lung cancer: 28%
- Lower respiratory infections: 27%
- Neonatal deaths: 13%

Top 5 Sources of Outdoor PM$_{2.5}$ and Associated Health Burden in Saudi Arabia in 2019

<table>
<thead>
<tr>
<th>Source</th>
<th>Residential</th>
<th>Industry</th>
<th>Energy</th>
<th>Anthropogenic Dust</th>
<th>Agriculture</th>
</tr>
</thead>
<tbody>
<tr>
<td>Contribution to total outdoor PM$_{2.5}$</td>
<td>1%</td>
<td>7%</td>
<td>15%</td>
<td>2%</td>
<td>3%</td>
</tr>
<tr>
<td>Number of PM$_{2.5}$ linked deaths</td>
<td>170</td>
<td>1,189</td>
<td>2,549</td>
<td>340</td>
<td>510</td>
</tr>
</tbody>
</table>

For More Information:
For the full report and additional data, please visit [www.msaqi.org](http://www.msaqi.org)

Additional Resources:
For real-time air quality data, visit [OpenAQ](http://openaq.org)
For more details, please visit [www.msaqi.org](http://www.msaqi.org)
Contact us: [contactus@healthfacts.org](mailto:contactus@healthfacts.org)

The State of Global Air website is a collaboration between the Health Effects Institute and the Harvard T.H. Chan School of Public Health, with expert input from The University of British Columbia.

Appendix Figure 3.

Agarwal, K. S., Mughal, M. Z., Upadhyay, P., Berry, J. L., Mawer, E. B., & Puliyel, J. M. (2002). The impact of atmospheric pollution on vitamin D status of infants and toddlers in Delhi, India. *Archives of Disease in Childhood*, 87(2), 111–113. https://doi.org/10.1136/adc.87.2.111


Zon, R. (1935). Possibilities of Shelterbelt Planting in the Plains Region: A Study of Tree Planting for Protective and Ameliorative Purposes as Recently Begun in the Shelterbelt Zone of North and South Dakota, Nebraska, Kansas, Oklahoma, and Texas by the Forest Service; Together with Information as to Climate, Soils, and Other Conditions Affecting Land Use.