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Is Air Pollution as Causal or Trigger Factor for Multiple Sclerosis?

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Abstract

Climate change, primarily driven by global warming and heightened air pollution, poses a significant threat to global health, particularly impacting neurological well-being. The present narrative review focuses on air pollution´s implications for patients with multiple sclerosis (MS). Individuals with MS, a chronic, inflammatory, demyelinating, and neurodegenerative disease of the central nervous system, experience heightened neurological symptoms exacerbations that correlate with exposure to air pollutants (PMs, UFPs, CO, NOx, NO_2, SO3, O_3). The mechanisms involve many immune-mediated interactions between genes and the environment that cause the blood-brain barrier to not work properly. This leads to neuroinflammation, more tissue damage, and the buildup of demyelinating lesions. In summary, air pollution compounds neurological manifestations and potentially contributes to their development through multifaceted pathways. Addressing the complex interactions between air pollution and MS requires intensified research and targeted strategies. A thorough understanding of climate change's neurological effects is crucial for effective public health interventions.

Keywords: Air Pollution; Multiple Sclerosis; Climate Change; Excitotoxicity; Neuroinflammation; Oxidative stress; Particulate Matters' Reactive Oxygen Species

Introduction

Climate change is commonly defined as a sequence of prolonged alterations in global temperature, weather patterns, and the composition of the Earth's atmosphere. These changes are primarily linked to the escalation of global warming caused by the higher levels of carbon emissions released into the atmosphere, which in turn results in a greenhouse effect. This phenomenon is both directly and indirectly connected to human activities [1]. Climate change is presently regarded as the most significant threat to global health in the 21st century [2]. The adverse effects also extend to the global economy, with an estimated cost of around $343 billion USD in 2021 [3].

According to experts, the countries most susceptible to the repercussions of climate change are those that are least developed. This vulnerability is primarily attributed to factors such as inadequate infrastructure, deficient healthcare systems, insufficient preventive measures, and limited access to sanitation facilities. Mexico, classified as a developing nation, has been identified as one of the countries facing a vulnerability to climate change ranging from 31% to 60%. This vulnerability is largely attributed to the average temperature increase of 0.85°C to 1.3°C since the 1960s, with approximately 71% of its population being highly exposed to the impacts of climate change [2].

Among the primary outcomes of climate change, the statistics underscore its effects on various health issues, including infectious diseases, respiratory ailments, cardiovascular disorders, neurological conditions, nutritional deficiencies, skin problems, allergies, and occupational illnesses [3]. Climate change is also recognized as a contributing factor that diminishes the well-being and health of individuals with comorbidities, primarily through exposure mechanisms, direct interactions with climatic factors, and indirect influences tied to demographic, economic, and social determinants [4].

As per the World Health Organization (WHO), neurological disorders result in roughly 6 million fatalities annually, with approximately 80% of these occurring in low- and middle-income countries. Recent research has underscored the significance of the connection between neurological disorders and climate change [5]. The Global Burden of Diseases (GBD) Study Group has stated that neurological diseases are responsible for the largest cause of disability-adjusted life years [6]. The global prevalence of MS has increased since 2013, and it is estimated that 2.8 million people are living with MS worldwide, with a prevalence rate of 35.9 per 100,000 population [7]. The prevalence of MS varies among high-income countries, with developed countries generally having higher prevalence rates compared to developing countries. For example, in developed countries like Canada, the prevalence rate of MS is 168 cases per 100,000 population, while in developing countries like Maldives, the prevalence rate is 1.52 cases per 100,000 population [8]. Currently, there is evidence to suggest that air pollution might affect MS. The exposition to polluted air has been linked to several mechanisms that act as risk factors for MS, as well as for relapses and neurological disability in individuals with the disease [9,10,11]

The purpose of this review is to analyze and describe the implications of air pollution and its chemical molecules (PM10, PM2.5, NO_2, O_3, Rn) and MS in the last decade.

Materials and Methods

We searched for scientific publications in English and Spanish listed in MEDLINE (PubMed), electronic databanks of Elsevier Bibliographic Database (Scopus) and Embase from January 2013 to August 2023. We used the following Medical Subject Headings (Mesh) search terms: (“Autoimmune Diseases” OR “Autoimmune Disease” OR "Multiple Sclerosis" OR "MS" OR “Encephalitis” AND “Air Pollution” OR “Air Pollutants” OR ”Air Quality Index” OR “Particulate Matter” OR “PM” OR “PM2.5” OR “PM10” OR “Gaseous Pollutants” OR “Climate Change” OR “Nitrogen Oxides” OR “NOx” OR “Nitric Oxide” OR “NO” OR “Nitrogen Dioxide" OR “NO2” OR “Carbon Monoxide” OR “CO” OR "Radon" OR "Rn" OR "Radium" OR "Ra") to identify retrospective or prospective observational clinical studies in humans. We excluded commentaries, summaries, editorials, animal studies, toxicological studies, duplicates, and studies reporting associations unrelated to our research objectives. We included, at the beginning of the

neurological condition, articles of review or epidemiological studies that included data on the burden of the disease, its definition, and potential mechanism involved in the association between air pollution and the MS to provide a comprehensive overview. Ethical issues have been completely observed by the researchers.

Results

A total of 200 (Scopus 114 + PubMed 86) articles were obtained in the initial search from all above-mentioned databanks. Figure 1 show the flowchart of selection of scientific publications analyzed. Finally, 53 studies met the study criteria. In the next section, we will discuss the main findings of association between air pollution and MS.

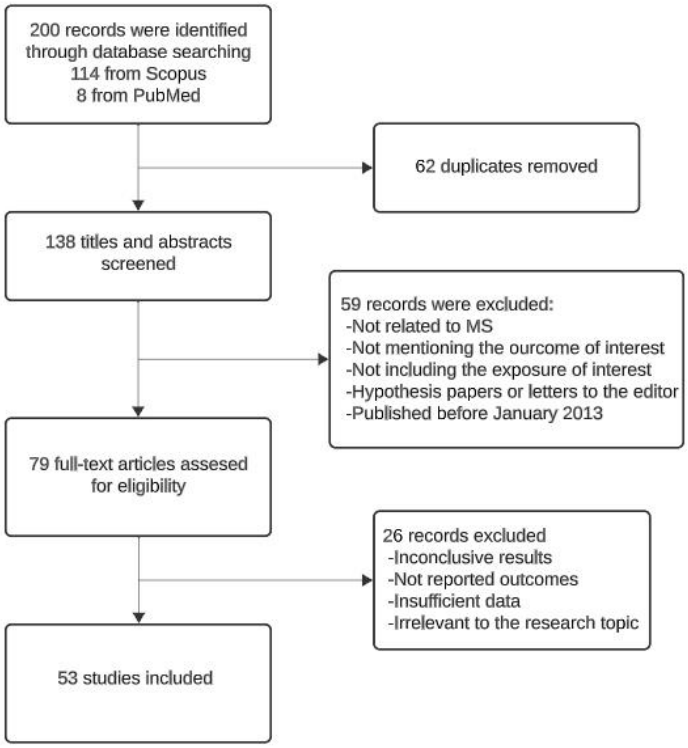


Figure 1: Flowchart of selection of scientific publications.

Multiple Sclerosis Brief Overview

MS is a chronic, inflammatory, demyelinating, and degenerative condition of the central nervous system that is characterized by multifaceted immune-mediated interactions between genes and the environment (such as HLA-DRB1*15:01 haplotype, HLA--DR15/16 serotype group, IL2RA, IL17R, low vitamin D levels due to lack of sun exposure, child obesity, smoking, and latitudinal gradient) that provoke accumulation of demyelinating focal plaques, that occur in the white and gray matter of the brain and spinal cord [12-16]. Figure 2. The clinical presentation of MS is diverse and varies depending on the location of the lesions; the typical onset in nearly 85% of patients consists of unpredictable episodes of optic neuritis, myelitis, brainstem, and cerebellar syndromes, cerebral hemispheric syndromes, and/or pyramidal syndromes [12].

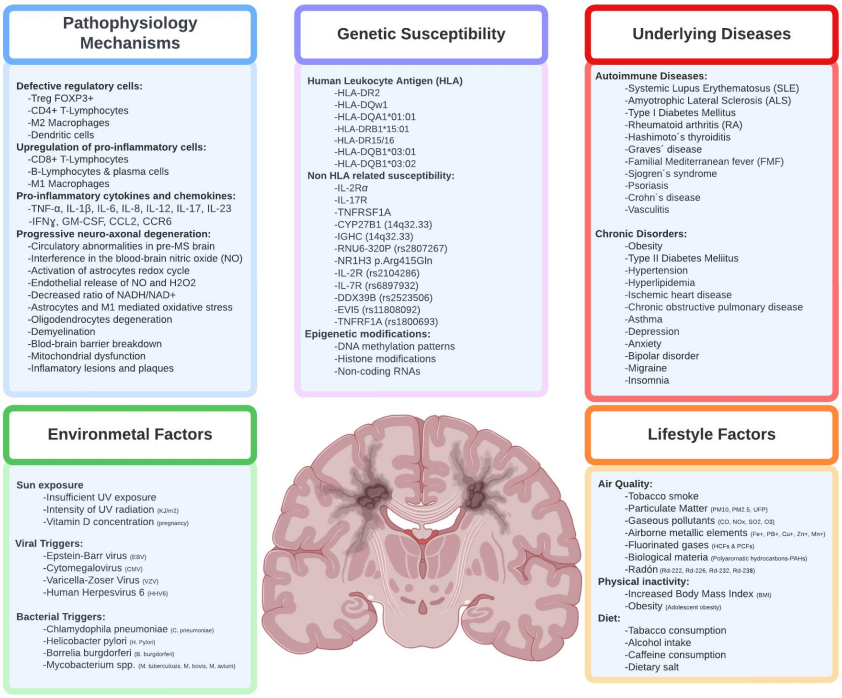


Figure 2: Pathophysiology Mechanism, Genetic Susceptibility, Underlying Diseases, Environmental Factors and Lifestyle Factors related to Multiple Sclerosis

MS, is the primary cause of non-traumatic disability in young adults between 20 and 40 years old, and is associated with a high societal economic burden, with approximately 2.3 million people affected worldwide (MSIF, 2013). In 2010, nearly 14.6 billion euros were invested in Europe [17], and in 2013, nearly 4.3 billion dollars were spent in the United States [18]. The hallmark of all MS phenotypes is the presence of focal plaque areas where demyelination occurs, typically found near post-capillary venules, and marked by the permeability disturbance of the blood-brain barrier (BBB) [13]. The exact mechanisms remain elusive but may involve the effects of pro-inflammatory cytokines and chemokines released by resident and endothelial cells (TNF- α, IL-1β, IL-2, IFNγ, GM-CSF, CCL2, and IL-6), along with indirect cytokine and chemokine-mediated damage caused by activated leukocytes [19]. Disturbances in the BBB permeability promote the movement of macrophages, T cells (CD4+ and CD8+), B cells, and plasma cells into the CNS, subsequent microglia, and astrocyte activation, exacerbating neuroinflammation and the demyelination process, followed by the loss of oligodendrocytes, reactive gliosis, the production of reactive oxygen and nitrogen species, and diffuse neuro-axonal degeneration [12,13,19,]. Figure 2. The reasons for the rising prevalence and incidence of MS worldwide are not fully understood Figure 2 [8,13].

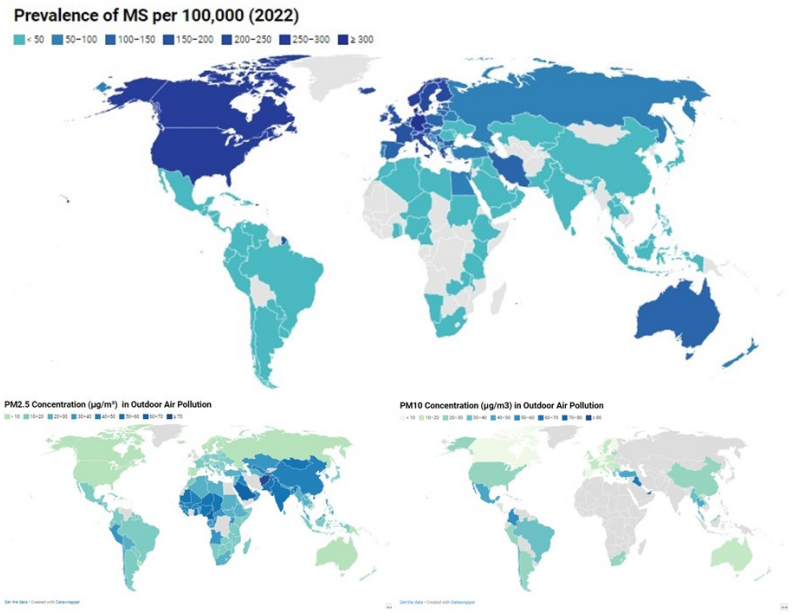


Figure 3: Correlation between Air Pollution and prevalence of MS. A) Prevalence of Multiple Sclerosis per 100,000 inhabitants (2022). Worldwide B) PM2.5 concentration (µg/m3) in outdoor air pollution, and C) PM10 concentration (µg/m3) in outdoor air pollution.

Risk Factors for MS and Air Pollution

In industrialized countries, the incidence of autoimmune disorders (AD) has consistently increased over the past century, suggesting that a change in their environment may be the cause of epidemiological observations [20]. Environmental factors could be responsible for 40–70% of all AD [21,22], and may contribute to an increased likelihood of MS and may be prevalent at a given time, thereby increasing the disease risk.

The interaction of genetic susceptibility, particularly HLA variants such as HLA-DRB1*15:01, and environmental factors, airborne pathogens, and sun exposure, appears to be the disease's primary cause, suggesting that there are shared pathways that cause this condition, especially when it comes to activating the immune system's response [23,24]. An increased concentration of ambient particulate matter (PM), one of the most studied components of air pollution, has been linked to both increased morbidity and mortality [25]. PM compromise solid particles, and liquid droplets, which can include acids, metals, soil, and dust. These particles are classified based on their aerodynamic diameter into PM10, PM2.5, and ultra-fine particles. Additionally, gaseous pollutants, containing carbon monoxide (CO), nitrogen oxides (NOx), sulfur dioxide (SO2), and ozone (O3), are usually emanated from transportation system and fossil fuel combustion [26]

The extent of damage usually depends on the time exposed to toxic air pollutants and the concentration of toxic pollutants. There are several pathways to the toxic air pollutants interact with the human body through lungs, mucous membranes of the eyes, ears, nose and gastrointestinal tract and skin [11]. One of the most recognizable theories is the "lung hypothesis," which posits that inflammation in the lungs or alterations to proteins through post-translational modifications induce local and systemic highly immunogenic antigens. These antigens, in turn, trigger autoimmune diseases or a non-specific inflammatory response, lowering the threshold for the development of multiple sclerosis or autoimmunity [27].

A substantial amount of research supports a period of susceptibility to environmental triggers for MS throughout adolescence, although exposure to certain risk factors may be relevant throughout different stages of development [12].

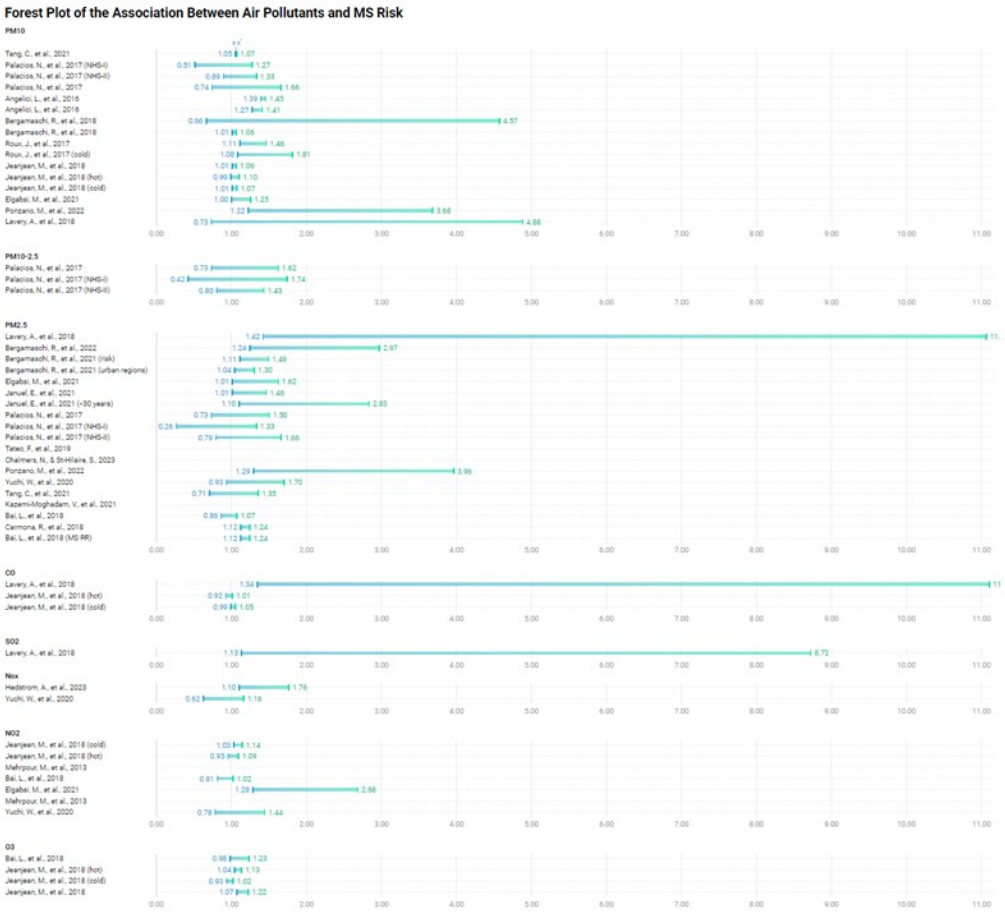


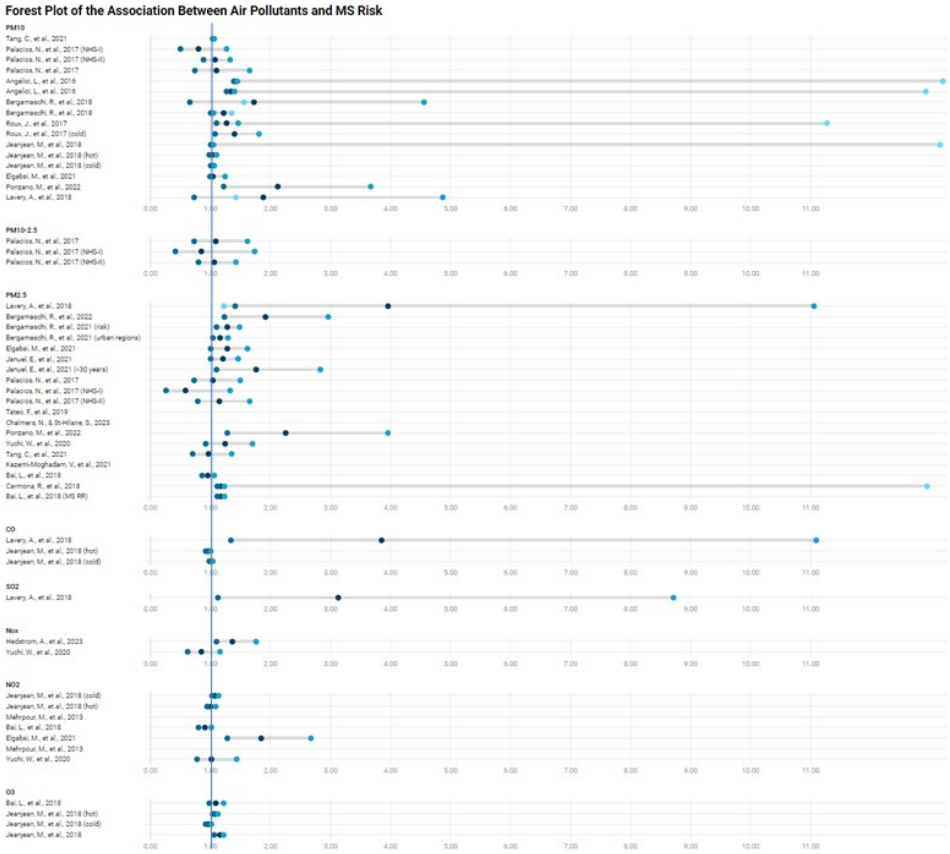
Figure 4: Forest Plot of the Association between Environment Variables and MS risk

Physiopathology of the Effect of Air Pollutants in MS

The inhalation of pollution-related biochemical indicators (PM2.5, PM10, SO2, NO2) increases oxidative stress along with epithelial wall permeability, leads to the production of pro-inflammatory cytokines, and induces an immune response by stimulating potentially auto-reactive T cells to migrate to the CNS, and post-translational modifications such as methylations of proteins and DNA with the potential to initiate and exacerbate autoimmune disorders [11].

The outcomes of the present research conducted by Cortese, A., et al., (2020) suggest that air pollution may contribute to MS inflammatory processes through two distinct mechanisms: PM10 might directly lead to upward regulation of CCR6 on circulating lymphocytes, which could promote their passage into the CNS; and PM10 might boost IL1-β, IL6, and IL23 production by dendritic cells (DC) thereby improving DC-dependent expression of IL17-producing T cells [20].

Air pollution is also caused by the presence of an assortment of different types of chemicals in the environment or indoor atmospheres, such as gaseous pollutants (CO, ozone [O3], NOx and sulfur oxides [SOx]), PM 10 (coarse particles), fine particles (PM2.5), very fine particles (PM1) and ultrafine particles/UFPs [PM0.1, <100 nn]), airborne metallic elements (Fe+, Pb+, Cu+, Zn+, Mn+) and biological material (bioaerosol and polyaromatic hydrocarbons [PAHs]) [11,28,29,30]. A systematic literature review by Noorimotlagh, Z., et al. examined 19 studies that reported a significant association between air pollutions exposure (PM10, PM2.5, O3, SO2, NO2, NO, NOx, CO2, CO, Radon gas) and MS, and 15 of these papers discussed the potential effects [31] as is mentioned in the Figure 2.


Forest Plot of the Association Between Air Pollutants and MS Risk
PM10
Tang, C., et al., 2021
Palacios, N., et al., 2017 (NHS-I)
Palacios, N., et al., 2017 (NHS-II)
Palacios, N., et al., 2017
Angelici, L., et al., 2016
Angelici, L., et al., 2016
Bergamaschi, R., et al., 2018
Bergamaschi, R., et al., 2018
Roux, J., et al., 2017
Roux, J., et al., 2017 (cold)
Jeanjean, M., et al., 2018
Jeanjean, M., et al., 2018 (hot)
Jeanjean, M., et al., 2018 (cold)
Elgabsi, M., et al., 2021
Ponzano, M., et al., 2022
Lavery, A., et al., 2018
PM10-2.5
Palacios, N., et al., 2017
Palacios, N., et al., 2017 (NHS-I)
Palacios, N., et al., 2017 (NHS-II)
PM2.5
Lavery, A., et al., 2018
Bergamaschi, R., et al., 2022
Bergamaschi, R., et al., 2021 (risk)
Bergamaschi, R., et al., 2021 (urban regions)
Elgabsi, M., et al., 2021
Januel, E., et al., 2021
Januel, E., et al., 2021 (>30 years)
Palacios, N., et al., 2017
Palacios, N., et al., 2017 (NHS-I)
Palacios, N., et al., 2017 (NHS-II)
Tateo, F., et al., 2019
Chalmers, N., & St-Hilaire, S., 2023
Ponzano, M., et al., 2022
Yuchi, W., et al., 2020
Tang, C., et al., 2021
Kazemi-Moghadam, V., et al., 2021
Bai, L., et al., 2018
Carmona, R., et al., 2018
Bai, L., et al., 2018 (MS RR)
CO
Lavery, A., et al., 2018
Jeanjean, M., et al., 2018 (hot)
Jeanjean, M., et al., 2018 (cold)
SO2
Lavery, A., et al., 2018
Nox
Hedstrom, A., et al., 2023
Yuchi, W., et al., 2020
NO2
Jeanjean, M., et al., 2018 (cold)
Jeanjean, M., et al., 2018 (hot)
Mehrpour, M., et al., 2013
Bai, L., et al., 2018
Elgabsi, M., et al., 2021
Mehrpour, M., et al., 2013
Yuchi, W., et al., 2020
O3
Bai, L., et al., 2018
Jeanjean, M., et al., 2018 (hot)
Jeanjean, M., et al., 2018 (cold)
Jeanjean, M., et al., 2018
0.00
1.00
2.00
3.00
4.00
5.00
6.00
7.00
8.00
9.00
10.00
11.00

Summary of the Association Between Air Pollutants and MS Risk

Source	Variable	Study type	OR (95% CI)	x	x´	p	
Tang, C., et al., 2021	PM10	Systemic review and meta-analysis	1.06	1.05	1.07		
Palacios, N., et al., 2017 (NHS-I)	PM10	Cohort sturdy	0.80	0.51	1.27		
Palacios, N., et al., 2017 (NHS-II)	PM10	Cohort sturdy	1.08	0.89	1.33		
Palacios, N., et al., 2017	PM10	Cohort sturdy	1.11	0.74	1.66		
Angelici, L., et al., 2016	PM10	Cohort sturdy	1.42	1.39	1.45	<0.001	13.21
Angelici, L., et al., 2016	PM10	Cohort sturdy	1.34	1.27	1.41	<0.001	12.93
Bergamaschi, R., et al., 2018	PM10	Cross-sectional study	1.73	0.66	4.57	0.262	1.56
Bergamaschi, R., et al., 2018	PM10	Cross-sectional study	1.23	1.01	1.06	0.686	1.36
Roux, J., et al., 2017	PM10	Case-control study	1.27	1.11	1.46	<0.001	11.28
Roux, J., et al., 2017 (cold)	PM10	Case-control study	1.40	1.08	1.81		
Jeanjean, M., et al., 2018	PM10	Case-crossover study	1.03	1.01	1.06	0.043	13.16
Jeanjean, M., et al., 2018 (hot)	PM10	Case-crossover study	1.04	0.99	1.10		
Jeanjean, M., et al., 2018 (cold)	PM10	Case-crossover study	1.04	1.01	1.07		
Elgabsi, M., et al., 2021	PM10	Case-crossover study	1.05	1.00	1.25		
Ponzano, M., et al., 2022	PM10	Case-control study	2.12	1.22	3.68		
Lavery, A., et al., 2018	PM10	Case-control study	1.88	0.73	4.88	0.183	1.43

Palacios, N., et al., 2017	PM10-2.5	Cohort study	1.09	0.73	1.62		
Palacios, N., et al., 2017 (NHS-I)	PM10-2.5	Cohort sturdy	0.85	0.42	1.74		
Palacios, N., et al., 2017 (NHS-II)	PM10-2.5	Cohort sturdy	1.07	0.80	1.43		
Lavery, A., et al., 2018	PM2.5	Case-control study	3.96	1.42	11.06	0.009	1.22
Bergamaschi, R., et al., 2022	PM2.5	Multivariate analysis	1.92	1.24	2.97	0.003	
Bergamaschi, R., et al., 2021 (risk)	PM2.5	Ecological study	1.29	1.11	1.49	<0.001	
Bergamaschi, R., et al., 2021 (urban regions)	PM2.5	Ecological study	1.16	1.04	1.30	0.003	
Elgabsi, M., et al., 2021	PM2.5	Case-crossover study	1.28	1.01	1.62		
Januel, E., et al., 2021	PM2.5	Retrospective case-crossover study	1.21	1.01	1.46		
Januel, E., et al., 2021 (<30 years)	PM2.5	Retrospective case-crossover study	1.77	1.10	2.83		
Palacios, N., et al., 2017	PM2.5	Cohort sturdy	1.04	0.73	1.50		
Palacios, N., et al., 2017 (NHS-I)	PM2.5	Cohort sturdy	0.59	0.26	1.33		
Palacios, N., et al., 2017 (NHS-II)	PM2.5	Cohort sturdy	1.15	0.79	1.66		
Tateo, F., et al., 2019	PM2.5	population-based cross-sectional study				<0.001	
Chalmers, N., & St-Hilaire, S., 2023	PM2.5	Ecological study				<0.0014	

Ponzano, M., et al., 2022	PM2.5	case-control study	2.26	1.29	3.96		
Yuchi, W., et al., 2020	PM2.5	Nested case-control study	1.25	0.93	1.70		
Tang, C., et al., 2021	PM2.5	systemic review and meta-analysis	0.98	0.71	1.35		
Kazemi-Moghadam, V., et al., 2021	PM2.5	Ecological study				>0.05	
Bai, L., et al., 2018	PM2.5	Cohort study	0.96	0.86	1.07		
Carmona, R., et al., 2018	PM2.5	Cohort study	1.18	1.12	1.24	<0.001	12.95
Bai, L., et al., 2018 (MS RR)	PM2.5	Cohort study	1.18	1.12	1.24		
Lavery, A., et al., 2018	CO	Case-control study	3.85	1.34	11.10		
Jeanjean, M., et al., 2018 (hot)	CO	Case-crossover study	0.97	0.92	1.01		
Jeanjean, M., et al., 2018 (cold)	CO	Case-crossover study	1.02	0.99	1.05		
Lavery, A., et al., 2018	SO2	Case-control study	3.14	1.13	8.72		
Hedstrom, A., et al., 2023	Nox	two population-based case-control study	1.37	1.10	1.76	p=0.0001	
Yuchi, W., et al., 2020	Nox	Nested case-control study	0.85	0.62	1.16		
Jeanjean, M., et al., 2018 (cold)	NO2	Case-crossover study	1.08	1.03	1.14		
Jeanjean, M., et al., 2018 (hot)	NO2	Case-crossover study	1.01	0.95	1.09		
Mehrpour, M., et al., 2013	NO2	Ecological time series sturdy				p=0.03	
Bai, L., et al., 2018	NO2	Cohort sturdy	0.91	0.81	1.02		
Elgabsi, M., et al., 2021	NO2	Case-crossover study	1.85	1.28	2.68		
Mehrpour, M., et al., 2013	NO2	Time-series study				P=0.03	
Yuchi, W., et al., 2020	NO2	Nested case-control study	1.02	0.78	1.44		
Bai, L., et al., 2018	O3	Cohort sturdy	1.09	0.98	1.23		
Jeanjean, M., et al., 2018 (hot)	O3	Case-crossover study	1.08	1.04	1.13		
Jeanjean, M., et al., 2018 (cold)	O3	Case-crossover study	0.97	0.93	1.02		
Jeanjean, M., et al., 2018	O3	Case-crossover study	1.16	1.07	1.22		
Abaszadeh-Fathabadi, Z., et al., 2020	Rd	case-control study				p = 0.882	

Summary of the Association Between Air Pollutants and MS Risk

Source	Variable	Study type	OR (95% CI)	x	x'	p
Tang, C., et al., 2021	PM10	Systematic review and meta-analysis	1.06	1.05	1.07	
Palacios, N., et al., 2017 (NHS-I)	PM10	Cohort sturdy	0.80	0.51	1.27	
Palacios, N., et al., 2017 (NHS-II)	PM10	Cohort sturdy	1.08	0.89	1.33	
Palacios, N., et al., 2017	PM10	Cohort sturdy	1.11	0.74	1.66	
Angelici, L., et al., 2015	PM10	Cohort sturdy	1.42	1.39	1.45	<0.001
Angelici, L., et al., 2015	PM10	Cohort sturdy	1.34	1.27	1.41	<0.001
Bergamaschi, R., et al., 2018	PM10	Cross-sectional study	1.73	0.66	4.57	0.262
Bergamaschi, R., et al., 2018	PM10	Cross-sectional study	1.23	1.01	1.86	0.686
Roux, J., et al., 2017	PM10	Case-control study	1.27	1.11	1.46	<0.001
Roux, J., et al., 2017 (cold)	PM10	Case-control study	1.40	1.08	1.81	
Jeanjean, M., et al., 2015	PM10	Case-crossover study	1.03	1.01	1.06	0.049
Jeanjean, M., et al., 2015 (hot)	PM10	Case-crossover study	1.04	0.99	1.10	
Jeanjean, M., et al., 2015 (cold)	PM10	Case-crossover study	1.04	1.01	1.07	
Elgabal, M., et al., 2021	PM10	Case-crossover study	1.05	1.00	1.25	
Ponzano, M., et al., 2022	PM10	Case-control study	2.12	1.22	3.68	
Lavery, A., et al., 2018	PM10	Case-control study	1.88	0.73	4.88	0.183
Palacios, N., et al., 2017	PM10-2.5	Cohort study	1.09	0.73	1.62	
Palacios, N., et al., 2017 (NHS-I)	PM10-2.5	Cohort sturdy	0.85	0.47	1.74	
Palacios, N., et al., 2017 (NHS-II)	PM10-2.5	Cohort sturdy	1.07	0.80	1.43	
Lavery, A., et al., 2018	PM2.5	Case-control study	3.96	1.42	11.06	0.009
Bergamaschi, R., et al., 2022	PM2.5	Multivariate analysis	1.92	1.24	2.97	0.003
Bergamaschi, R., et al., 2021 (risk)	PM2.5	Ecological study	1.29	1.11	1.49	<0.001
Bergamaschi, R., et al., 2021 (urban regions)	PM2.5	Ecological study	1.16	1.04	1.30	0.008
Elgabal, M., et al., 2021	PM2.5	Case-crossover study	1.28	1.01	1.62	
Januel, E., et al., 2021	PM2.5	Retrospective case-crossover study	1.21	1.01	1.46	
Januel, E., et al., 2021 (<70 years)	PM2.5	Retrospective case-crossover study	1.77	1.10	2.83	
Palacios, N., et al., 2017	PM2.5	Cohort sturdy	1.04	0.73	1.50	
Palacios, N., et al., 2017 (NHS-I)	PM2.5	Cohort sturdy	0.59	0.26	1.33	
Palacios, N., et al., 2017 (NHS-II)	PM2.5	Cohort sturdy	1.15	0.79	1.66	
Talaei, F., et al., 2019	PM2.5	population-based cross-sectional study				<0.001
Chalmers, N., & Shillitoe, S., 2022	PM2.5	Ecological study				<0.0014
Ponzano, M., et al., 2022	PM2.5	Case-control study	2.26	1.29	3.96	
Yuchi, W., et al., 2020	PM2.5	Nested case-control study	1.25	0.93	1.70	
Tang, C., et al., 2021	PM2.5	systematic review and meta-analysis	0.98	0.71	1.35	
Kazemi-Moghaddam, V., et al., 2021	PM2.5	Ecological study				<0.05
Bai, L., et al., 2018	PM2.5	Cohort study	0.96	0.86	1.07	
Carmona, R., et al., 2015	PM2.5	Cohort study	1.18	1.12	1.24	<0.001
Bai, L., et al., 2018 (MS only)	PM2.5	Cohort study	1.18	1.12	1.24	
Lavery, A., et al., 2018	CO	Case-control study	3.85	1.34	11.10	
Jeanjean, M., et al., 2015 (hot)	CO	Case-crossover study	0.97	0.92	1.01	
Jeanjean, M., et al., 2015 (cold)	CO	Case-crossover study	1.02	0.99	1.05	
Lavery, A., et al., 2018	SO2	Case-control study	3.14	1.13	8.72	
Hedstrom, A., et al., 2023	Nox	Swedish population-based case-control study	1.37	1.10	1.76	p=0.0001
Yuchi, W., et al., 2020	Nox	Nested case-control study	0.85	0.62	1.16	
Jeanjean, M., et al., 2015 (cold)	NO2	Case-crossover study	1.08	1.03	1.14	
Jeanjean, M., et al., 2015 (hot)	NO2	Case-crossover study	1.01	0.95	1.09	
Mehrpour, M., et al., 2013	NO2	Ecological time series study				p=0.03
Bai, L., et al., 2018	NO2	Cohort sturdy	0.91	0.81	1.02	
Elgabal, M., et al., 2021	NO2	Case-crossover study	1.85	1.28	2.68	
Mehrpour, M., et al., 2013	NO2	Time-series study				P=0.03
Yuchi, W., et al., 2020	NO2	Nested case-control study	1.02	0.78	1.44	
Bai, L., et al., 2018	O3	Cohort sturdy	1.09	0.98	1.23	
Jeanjean, M., et al., 2015 (hot)	O3	Case-crossover study	1.08	1.04	1.13	
Jeanjean, M., et al., 2015 (cold)	O3	Case-crossover study	0.97	0.93	1.02	
Jeanjean, M., et al., 2015	O3	Case-crossover study	1.16	1.07	1.22	
Abbaszadeh-Esfahaqali, Z., et al., 2020	Rd	Case-control study				p = 0.882

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Figure 5: Summary of the Association between Environment Variables and MS risk

List of Potential Effects of Air Pollutants

- •Untamed responses to inflammatory agents secondary to oxidative stress (OS) cause neurological inflammation and disruption of the average interaction stage between immunity and self-tolerance [32,33,34].
- •The unrestrained inflammatory reactions that comply result in cellular death and the release of self-antigens, which can stimulate the generation of autoreactive T-cells by improving the presentation of antigens and encouraging the access of autoreactive cells through the BBB [36,37].
- •Air pollution exposure may induce OS and promote the permeability of the epithelial cells, leading to the secretion of inflammatory cytokines and encouraging a defense response by triggering auto-reactive T cells and enhancing their passage to the CNS through the BBB [11,20,32,37].

- •The inhalation of PM could be translocated to the CNS via the olfactory system epithelia and accumulation of air pollutants trigger alveolar macrophages and endure chemical-based reactions that generate nitrogen reactive species (RNS) and reactive oxygen species (ROS) that are able to activate inflammatory signaling pathways through redox-sensitive mitogen-activated protein kinase (MAPK) alongside nuclear factor-κB (NF-κB), which are accountable for the expression of cytokines (TNFα, IL-1, , IL-6, IL-8), chemokines (CCR6), attachment molecules and prolonged activity leading to OS and cellular damage, such as peroxidation and oxidation of lipids and proteins, respectively, DNA/RNA modification, and recruiting neutrophils, monocytes/macrophages, and dendritic cells (DC) that initiates adaptive immune reactions involving Th1 and Th17 polarizing cytokines (IL-23, TGF-β, IL-6 and IL-1β), enhancing their inflammatory and migratory properties through the BBB and contributing to the immunopathogenesis of MS [11,20,31,38,39,40].

- •It was found that short-term exposure to PM2.5 could result in a reduction in methylation at CpG loci of the associated inflammation-related genes [41], upregulating the expression of cytokines (TNFα, IL-1, IL-6, IL-8), chemokines receptors (CCR6), adhesion molecules, and consequently contributing to the immunopathogenesis [11].

- •Significant variations were reported in the exposure to fine particulate matter (PM2.5) and 3 contaminants (CO, SO2, and Pb+) among MS patients and controls, suggesting that air pollution may be a contributory factor for MS by proinflammatory exacerbations [42].

Greenhouse Gas Emissions and Heat Exposure In MS

Air pollutants and greenhouse gases play crucial roles in climate change by contributing to rising temperatures. Carbon dioxide (CO_2), methane (CH_4), nitrous oxide (N_2O), and fluorinated gases (HCFs & PCFs) are the most significant contributors, with CO2 accounting for 79% of total emissions in the United States [43]. The influence of greenhouse gases on climate change is mediated by their ability to retain heat in the atmosphere. Solar energy reaches Earth's surface, which is absorbed and re-emitted as infrared radiation. These gases intercept this radiation, preventing it from escaping into space. This captured energy is reradiated in various directions, with a significant portion directed towards Earth, thereby warming the planet. As greenhouse gas concentrations increase, additional warmth is retained, causing the average surface temperature to rise over time [43].

Heat exposure can trigger a temporary exacerbation of MS symptoms in 60–80% of patients, known as Uhthoff's phenomenon [44,45]. Heat sensitivity in MS arises from the adverse impact of elevated temperatures on the propagation of action potentials in axons that lack myelin insulation, resulting in either slowed conduction or blockage. Furthermore, MS can lead to compromised regulation of autonomic and endocrine functions, like sensory impairments, altered neural processing within the central nervous system, impaired responses in effectors responsible for temperature regulation and control, affecting neural command over sudomotor pathways, and neural-induced changes in eccrine sweat glands [44].

A study of 1,254 MS patients directed by Stellmann et al. revealed that an increase in ambient temperature of 10°C could exacerbate mobility deficits in MS patients, whereas hand function, cognition, mood, and fatigue do not appear to be correlated with fluctuations in ambient temperature [45].

Byun, S., et al. (2020), who conducted a time-stratified case-crossover study in Korea from January 2008 to December 2014, found that exacerbations were associated with increased temperature variability on the previous day, with an 8.81% increase in reports per 1°C increase in range (95% CI: 3.46–14.44) [46].

A retrospective cohort study directed by Elser, H., et al., (2021) analyzed through the Optum database 75,395,334 individuals, of whom 106,225 had a positive diagnosis of MS and were followed for a total of 3,785,229 months. The results concluded that there was limited evidence of an association between anomalously warm weather and MS-related outpatient visits (RR = 1.010, 95% CI: 1.005 to 1.015) and inpatient visits (RR = 1.032, 95% CI: 1.010 to 1.054), providing preliminary evidence that high temperatures in-

crease the risk of MS-related hospital admissions [47].

In conclusion, elevated temperatures do not directly trigger the autoimmunity of MS and do not directly contribute to the pathogenesis of the aforementioned neurodegenerative disorder; nevertheless, they increase manifestations through mechanisms that involve many immune-mediated interactions between genes and the environment [48].

Association between PM and Multiple Sclerosis

PM10 can come from both primary and secondary sources. Primary sources cause particle pollution on their own, while secondary sources emit gases that can form particles [49].

- •Primary Sources: Wood combustion, construction sites, manufacturing facilities, and vehicles [49].
- •Secondary Sources: Power plants emissions, industrial facilities, and internal combustion engine vehicles [49].

Several studies have investigated the association between air pollution, including PM10 and PM2.5, and MS development and progression. A systematic review found a significant relationship between exposure to air pollution and MS development and progression [31,50,51].

A scoping review conducted by Louis, S., et al., (2023) identified 364 articles related to climate change and air pollution on neurologic health, of which only 19 addressed the correlation between air pollution (specifically PM) and MS; 5 research investigations took place in Asia, 11 on the European continent, and 3 in North America to examine the relationship between MS incidence and environmental exposures to air pollutants (PM2.5, PM10, SO2, NO2, O3, and benzene) [52]. Figure 2. Nevertheless, conclusive correlations between ongoing ambient contaminant exposure and the incidence of MS have not been demonstrated, and several studies have not accounted for recognized risk variables, including sunlight intake or familial susceptibility [52]. Other investigations analyzed both the short- and long-term hazards linked to ambient contaminants on the development of MS and hospital admissions related to the disease [53,54,]. Overall, the short-term interaction with ambient contaminants was associated with worsening symptoms [53,54].

The findings of Farahmandfard et al's systematic review indicate that pollution from the environment, particularly PM and nitrogen oxides (NOx), may be associated with prevalence or recurrence of MS [55]. In Tehran, Iran prevalent MS cases exhibited a clustering pattern. Statistically significant differences in exposure to PM10, SO2, NO2, and NOx were identified between MS cases and controls ($p<0.001$) [56].

Relating to Air Quality Index (AQI), Ashtari, F., et al. indicated that air pollution may influence the severity and regression of MS disease. AQI score was correlated with the degree of full recovery after the initial complication, OR=1.005 (95% CI=1.004-1.006) [33]. Air pollution has also been associated with lower scores on the MS expanded disability status scale (EDSS), lower rates of MS remission, greater MS severity, and inferior recovery from the initial MS event [33]. Heydarpour et al. found a statistically significant variance in the exposure to PM10 among MS patients and controls, implying that long-term exposure to air contaminants may be an environmental risk factor in MS [56].

The outcomes of a systemic review and meta-analysis of 461 citations, where only 6 studies were included [18,28,36,37,57,58] revealed that only PM10 was associated with MS (pooled HR = 1.058, 95% CI = 1.050–1.066) [59].

In pediatrics, emissions of airborne pollutants have been associated with a higher risk of MS ($p<0.01$) for individuals living within 20 miles of an MS center; PM2.5, OR=3.96 (95% CI: 1.42–11.10), CO, OR=3.85 (95% CI: 1.34–11.10), along with SO2, OR=3.14 (95% CI: 1.13–8.72) [42].

Between April 2014 and June 2015, a door-to-door population-based study was undertaken in two localities in Turkey (Karabük and Akcakoca) to examine the prevalence percentages of MS and its potential association with airborne contaminants (PM10, SO2, NO2, Zn2+, Cd2+, Cu2+, Cr3+, Pb2+, Fe2+, Mn2+, Ni2+) in proximity to an iron-and-steel factory. According to the outcomes, the median prevalence of MS in Karabük, the municipality in direct proximity to the iron-and-steel manufacturing facility, was 107.1/100,000 In Akcakoca, a coastal city situated 100 km from Karabük, the rate was 41.5/100,000 [35].

Negative Studies about the Relation between PMS and MS

The overall number of relapses reported in a study by Vojinovi, S., et al., was significantly negatively correlation with the number of days with NSR (air pollution conveyed as new source review) <2 (rspearman=0.31; p<0.01), suggesting an upsurge in recurrent episodes throughout intervals with a limited number of days that had low air pollution [32].

Bai, L., et al., reported a lack of correlation between the incidence of MS and long-term exposition to PM2.5 (OR 0.96 95% [CI 0.86–1.07]), NO2 (OR 0.91 95% [CI 0.81–1.02]), or O3 (OR 1.09 95% [CI 0.98–1.23]) [57]. Regarding Highways and major traffic roads was found no correlation involving traffic-related chemical contaminants and diagnoses for MS [59]. Tang´s meta-analysis suggests that, except for PM10, there is no statistically significant association between MS development-progression with PM2.5 (10 μg/m3), PM2.5-10 (per 10 μg/m3), C6H6 (1 μg/m3), CO (50 μg/m3), NO (10 ppb), and O3 (10 ppb) [60].

Neither of two large cohort studies (Nurses Health Study/NHS: n=121,700 & Nurses Health Study II/NHS II: n=116,671) found a significant association between air pollutants and MS, HRs contrasting the top versus bottom quintiles of PM were 1.11 for PM10 (95% CI: 0.74-1.66) 1.04 for PM2.5 (0.73-1.5) and 1.09 for PM2.5–10 (0.73-1.62) [28]. Another study found no connection between PM and an increased likelihood of MS hospital admissions [59].

Several additional investigations have produced results that contradict the hypothesis of a direct correlation between MS onset and air pollutants. A recent Canadian study found no association between air pollutants and the incidence of MS [37]. Other studies have found no link between MS risk and PM2.5 [37,42,57], PM10 [28,61], NO2, nor O3 [57]. Chen et al. (2017) additionally observed no association between residing near intense traffic and the incidence of MS case [18].

Based on the outcomes of the research reviewed, it is hypothesized that air pollution is a risk factor for the onset and relapse of MS through the interaction and function of the immune system with inconclusive evidence.

PM10 and MS

Multiple adult MS reports have identified an association between elevated PM10 exposure of a higher risk [36,56,58] of MS relapsing [32,34,36,50,56,58,62].

A study conducted in Lombardy (Italy) analyzed 8287 MS-related hospitalizations. The results revealed a correlation between admissions for MS and exposure to PM10, with the greatest effect of PM10 occurring within days 0 and [36]. A case-crossover study involving 254 individuals and 1153 relapsing episodes took place in France; discovering a significant association between PM10 exposure in the 3 days prior to the relapse episode and the incidence of relapsing [63]. Also, hospital stays for MS increased by OR=1.42 (95% CI: 1.39-1.45) on days preceding a week with PM10 concentrations in the highest quartile [36].

Cortese et al. 2020 examined the amount of expression of markers implicated in T lymphocyte triggering, attachment, and migration using flow cytometry in 57 MS individuals and 19 healthy controls [20]. MS patients exhibited an association between mean concentrations of PM10 and the level of activity of C–C chemokine receptor 6 (CCR6) on CD4+T cells. They hypothesized that PM could possess a pro-inflammatory role in MS by increasing CCR6 expression on CD4+T cells [20].

Another study analyzed the days preceding cerebral MRI and found that there was evidence of a significant correlation between

Gadolinium + MRI and PM10 levels (OR=1.021 95% [CI: 1.00- 1.04] p=0.013), regardless of immune therapies, smoking status, and season. In individuals who underwent two consecutive MRIs with contrary results (Gd-MRI and Gd + MRI), PM10 levels were significantly elevated in conjunction with Gd+MRI (p<0.0001) [64].

Regarding colder temperatures and MS relapsing, studies such as Roux and Jeanjean´s analyzed the natural logarithm of the mean the amount of PM10 lagged from 1 to 3 days prior to relapsing onset had a significant correlation with recurrence risk (OR=1.40 [95% CI: 1.08–1.81]) [62], while from October to March, a spike in both NO2 and PM10 pollution (lags 0–3) was linked to MS resurgence (OR=1.08; 95% CI: [1.03–1.14] and OR=1.06; 95% CI: [1.01–1.11], respectively) [58].

According to a study conducted in France, an increase in MS relapses coincided with PM10 concentrations during the winter season by 6% (OR = 1.06; 95%CI: [1.01–1.11]) [58]. An Italian investigation discovered a 42% increase in MS hospitalizations in the week preceding PM10 concentrations in the highest quartile [32]. Elgabsi and his colleagues used a case-crossover method to look at the links between severe to moderate relapses in 287 people with MS and their exposure to air pollution and weather conditions. They found that relapses were linked with higher concentrations of PM10 (OR=1.05, 95%CI:1.00-1.25) [65].

A case-control investigation into the relationship between MS patients who have been exposed to PM2.5, PM10, and NO2 for an extended period of time and the severity of Covid-19. Risk has been found to be positively correlated with higher concentrations of PM10 (CI 95% OR=2.12 [1.22–3.68]) [66].

Negative Studies about the Relation between PM10 and MS

Even though the Total Environmental Quality Index (EQI), including PM10, is used in order to evaluate air quality, it was found that had no significant correlation with the likelihood of MS (p=0.90 for MS for <20 miles from center; p=0.43 for 20 miles); despite this, deteriorating air quality significantly increased the probabilities of MS in residents who lived nearby an referral facility (OR=2.83; 95% CI 1.50, 5.40) while those who resided ≥20 miles away from them (OR=1.61; 95% CI: 1.20–2.30) [61].

Multiple sclerosis incidence did not correlate with proximity to major roadways. (OR=1.02 95% CI 0.95–1.09) for those residing less than fifty meters from a busy traffic road, HR=0.93 (0.86–1.01) for those living between 50 and 100 meters, HR=1.01 (0.95–1.08) between 101 and 200 meters, and HR=1.01 (0.94–1.08) for the ones who reside between 201 and 300 meters [18].

PM2.5 and MS

PM2.5 may act as a risk factor for MS since PM2.5 may propagate into systemic circulation after entering through the alveoli and trigger systemic inflammatory processes across multiple tissues via proinflammatory reactions, impairment of the immune system, and mitochondrial damage, destroying the myelin sheaths and altering the BBB permeability [67].

According to Tateo et al., a population-based cross-sectional study found that the prevalence of MS was greater in metropolitan regions of Italy, and that this prevalence had a significant correlation with the median annual concentration of PM2.5 (r=0.81, p0.001) (Tateo, F., et al., 2019). It was additionally discovered that urban dwellers were more exposed to PM2.5 (22.41.2 g/m3) than those who resided in small towns, manufacturing regions, and rural locations. Later in an analysis of regression, Tateo et al. observed that the prevalence of MS was strongly correlated with exposure to PM2.5 (β=0.11, p<0.001) [67].

Bergamaschi, R., et al. executed a multivariate analysis on 1,087 individuals and found that elevated PM2.5 concentrations increased the risk of a worsening COVID-19 outcome. High levels of PM2.5 were significantly correlated (95%, OR=1.92 [1.24–2.97], p=0.003) with a higher probability of developing a less favorable COVID-19 prognosis in MS patients [68].

Elgabsi et al., in their study employing a case-crossover approach, conducted an analysis to investigate the relationships between the occurrence of moderate to severe relapses in 287 individuals with MS and their exposure to air pollution as well as meteorologi-

cal conditions, where PM2.5 was independently correlated with MS relapses in the nonsmoking individuals (CI 95% OR=1.28 [1.01-1.62]) [65].

Ecological research in counties of the United States with cooler winters revealed a significant positive correlation between the mean PM2.5 index and the MS rate of mortality (p<0.0014, 95%) [69].

Levels of PM2.5 contributed to admissions to hospitals from January 2009 to December 2013, according to a retrospective case-crossover study that included 2,109 hospitalizations most likely related to MS relapse, where the average PM2.5 concentration was significantly correlated (95% OR = 1.21 CI [1.01–1.46]), with a greater association observed in patients under the age of 30 (95% OR = 1.77 CI [1.10–2.83]) [70].

A case-control study examining the correlation among a long-term exposition to PM2.5, PM10, and NO2 and the degree of severity of Covid-19 among individuals with MS. Greater probabilities of contracting Covid-19 pneumonia have been correlated greater concentrations of PM2.5 (95% OR =2.26 CI [1.29–3.96]) [66].

An ecological study was undertaken in Italy between 2010 and 2016 to examine the geographic distribution of MS risk throughout the region of Pavia, Italy, in relation to the concentrations of PM2.5 (>25 μg/m3). The research also compared Pavia to Oltrepò, a province exhibiting lower PM2.5 values. The study conducted by Bergamaschi et al. (2021) revealed that the average number of cases of MS in Pavia was 196.4 per 100,000 residents (95% CI [171.8–224.6]). In contrast, the incidence rate in Oltrepò was 157.9 per 100,000 individuals (95% CI [137.7–181.5] p = 0.027). Standardized morbidity ratios (SRM) in Pavia remained 1.14 (95% CI [1.04–1.25]), whereas in the Oltrepò domain, the SMR was 0.96 (95% CI: 0.87–1.03) (p = 0.0045), indicating a risk increase of 29% (95% OR = 1.29, CI: [1.11–1.49; p = 0.001]). Furthermore, urban regions had an elevated overall MS risk (95% OR = 1.16, CI: [1.04–1.30; p = 0.003]) [50].

A population-based cross-sectional study was to examine the correlation between PM2.5 levels (22.4±1.2μg/m3) along with the prevalence of MS. As of 31 December 2015, 1435 MS patients residing in the Province of Padua, the prevalence of MS was found to be significantly (p<0.0001) more prevalent in metropolitan areas, including Padua City (218.6/100,000; CI95%: 196.6–240.6, p<0.0001) as well as other urban regions (168.8/100,000 (CI95%: 157.8–179.8, p<0.0001), in contrast with isolated communities (116/100,000) or countryside areas The average PM2.5 concentration was additionally linked to MS cases in regression analysis (β=0.11, p<0.001) [67].

Negative Studies about the Relation between PM2.5 and MS

The outcomes of a systemic review and meta-analysis conducted by Tang et al., revealed that only PM2.5 has no significant association with MS [18,28,36,37,57]. No significant correlations were found between MS incidence, prevalence, and mortality and exposure to PM2.5 (p > 0.05) [71]. In accordance with the findings of Tang's meta-analysis, no statistically significant correlation is observed between the onset of MS and PM2.5 (10 μg/m3, 95% OR=0.977 CI [0.705–1.353]) [60].

Nevertheless, the present research was unable to establish a cause-and-effect relationship. Considering the correlation between PM2.5 and MS, there's considerable variation, and a definitive conclusion cannot be derived.

Gaseous Pollutants and Oxidative Stress Agents (NO_2, O_3, SO_2, CO)

Farahmandfard et al.'s systematic review indicate that pollution related to nitrogen oxides (NOx), may be associated with prevalence or recurrence of MS [55]. NO2 had a weak effect on MS (p=0.03, rspearman = 0.27) [34]. While a correlation on NO2 was linked to MS resurgence in cold seasons, O3 and MS recurrence during "warmer" seasons was found significant (OR=1.16; 95% CI: [1.07–1.22]) [58]. On other hand, Benzene (C6H6) and CO were neither significantly nor substantially associated with relapse of MS [58].

Heydarpour et al. found a statistically significant variance in the exposure to SO2, NO2, and NOx among MS patients and controls spanning the years 2003 to 2013, implying that long-term exposure to air contaminants may be an environmental risk factor in MS [56].

A two population-based case-control study with 6635 cases and 8880 controls investigated the relationship regarding air pollution, in particular NOx concentration, and the likelihood of developing MS and the possibility of interaction with the HLA-DRB1*15:01 allele, disclosing a dose-dependent association between 3-year standard NOx levels surpassing the 90th percentile (3-year average) (24.6 mg/m3) were significantly correlated (95%, OR=1.37 CI [1.10–1.76], p=0.0001) when compared to levels beneath the 25th percentile (5.9 mg/m3) [72].

Elgabsi et al. conducted an analysis using a case-crossover approach to investigate the connections between the occurrence of severe to moderate relapses in 287 individuals with MS and their exposure to air pollution and meteorological conditions, finding a significant correlation with NO2 in all the MS patients (95% OR=1.85 CI [1.28-2.68]) [65]. A case-crossover study conducted from 2000 to 2009 on 424 MS patients residing in the Strasbourg region of France identified noteworthy single-pollution associations between MS relapses and exposures to NO2 (OR = 1.08; 95%CI: [1.03–1.14]) from October to March [58]. A time-series analysis of 160 individuals with MS reported in Iran revealed a moderate correlation (p=0.03, r=0.27) between NO2 levels and recurrent episodes of the disease, as measured by all air quality indicators [34].

Negative studies of association between Gaseous pollutants (NO_2, O_3, SO_2, CO) and MS

The results of Tang's meta-analysis indicate that there is no correlation that is statistically significant regarding the development of MS and gases such as CO (50 μg/m3), NO (10 ppb), and O3 (10 ppb) [60].

Environmental Radon (Rn) gas

As the most stable isotope, radon-222 is a radioactive gas characterized by being devoid of odor, color, and flavor. It is produced by the radioactive decay of actinium, uranium-238, and thorium-232, as well as radon-226 [73]. Radon is chemically inert but stands as the densest gas currently recognized. The element is detected in diverse concentrations in sediments, minerals, water, and soil. Furthermore, its outdoor and atmospheric concentrations differ considerably, even between seasons and locations, but range between 5 and 15 Bq/m3 (0.4 pCi/L) on average [73]. Being classified as a zero-valence element, it possesses a 3.8-day half-life and is chemically not as reactive as other radioactive isotopes, rendering it a valuable natural tracer in the realm of physical and biomedical research, but with a latent danger is due to its associated carcinogenic and proinflammatory characteristics [73,74,75,76,77]. There was no correlation between radon concentrations and MS incidence in an investigation undertaken during the autumn and winter seasons, according to the findings of a cross-sectional study assessed in Yazd, Iran [74].

Based on the results concentration of total Rn gas was higher in the homes of studied people, but according to EPA and WHO criteria were not significantly associated with the chance of MS [74]. Neither significant relationship with MS prevalence in a case--control study aimed to investigate indoor radon gas concentration in the homes of patients with MS (66.77 Bq/m3) and healthy individuals (65.33 Bq/m3) in Yazd City, Iran (p = 0.882) [78].

The lack of data to affirm or refute the proposed relationship between levels of radon and MS incidence was determined to be statistically insignificant by a study population comprising 20′140,498 person-years of monitoring [79].

Discussion

A growing body of evidence suggests a significant association between air pollution and the development and progression of MS [31,50,51]. However, the direct link between the presence of air pollution and increase of prevalence of MS is still inconsistent

across the studies [55,67,80].

The progression of MS is an intricate process comprising an assortment of genetic predisposition and environmental risk factors, with multiple variables interacting to trigger and exacerbate the illness; therefore, understanding the aforementioned variables possesses the potential to perform healthcare and prevention strategies, becoming essential for providing medical treatment and early detection for individuals who are at increased risk of developing MS or severe forms of MS .

Lifestyle and environmental variables interact with genetic factors to influence MS susceptibility and progression. Significantly, some environmental factors can be modified, research on the impact of latitude and migration provided the initial indicators of environmental influences, is known for a long time that there is a latitudinal gradient in MS, with the disease being more prevalent the further from the equator [80]. Research on migration has demonstrated that individuals who migrate from a nation with a significant risk to a relatively low-risk region before adolescence exhibit a lower illness rate, while individuals who migrate from a low-risk country to a land with a high-risk level develop an increased probability of developing a determined condition [81].

Determining the significance of lifestyle or environmental variables in the development of MS is challenging, and large-scale prospective research efforts are required.

The escalating impact of air pollution and climate change, predominantly driven by global warming and increased carbon emissions, poses a substantial threat to global health, particularly the nervous system [12]. Various mechanisms intertwine climate change with the manifestations and exacerbations of neurological disorders [11,20]. This review has elucidated the profound implications of air pollutants and their impact on the presentation, manifestation, and progression of MS pathogenesis. Susceptibility to temperature changes due to its effects on demyelination, thermoregulation, and symptom exacerbation [44].

The intricate interplay between global warming, vector-borne infections, air pollution, and neurological health necessitates further research. Developing strategies to mitigate the impact of air pollution on neurological disorders is imperative, considering its potential to exacerbate symptoms and even contribute to disease development. Understanding these complex interactions is crucial for effective public health interventions, and there is an urgent need for comprehensive research to guide timely interventions for vulnerable populations.

Conclusion

There is a complex interaction between air pollution and MS. Air pollution promotes neuroinflammation through several mechanisms and increases the frequency of relapses and the severity of MS. However, additional prospective studies are needed to confirm its role in the etiology.

Highlights

- •Air pollution could be affecting the epidemiology of MS
- •Neuroinflammation induced by air pollution is involved in MS
- •Air pollution is related with relapses and worsening of MS
- •Genetic-Environmental interactions play a key role in MS

Declarations of Interest

None

Submission Statements

All authors have reviewed and agree with the contents of the manuscript. Daniel San-juan, M.D., MSc., the first author, takes full responsibility for the data, analyses, interpretation, and implementation of the research. Daniel San-juan, M.D., MSc., also had full access to all data; he has the right to publish any and all data separately and distinctly from any sponsor. We certify that the submission (aside from an abstract) is not under review at any other publication. All authors participated in a meaningful way in the preparation of the manuscript.

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