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Review

AIR POLLUTION AS A CONTRIBUTING RISK FACTOR OF RELAPSES AND CASES OF MULTIPLE SCLEROSIS

C. Zhukovsky[1], M.-A. Bind[2], I. Boström[3], A.-M. Landtblom[4]

[1]Department of Neurosciences, Uppsala University, 3 Husargatan Str., Uppsala, SE-752 36, Sweden
[2]Department of Statistics, Harvard University, MA 02138, Massachusetts Hall, Cambridge, USA
[3]Departments of Neurology and Clinical and Experimental Medicine, Linköping University, SE-581 83, Linköping, Sweden
[4]Uppsala University Hospital, SE-751 85, Uppsala, Sweden

The role of air pollution exposure in multiple sclerosis (MS) incidence and relapse worldwide has not yielded a consensus; some studies have reported positive associations, which have failed to reject the null hypothesis. Potential reasons for these contradictory results can in part be explained by differences in study designs and their associated limitations. Of note, rat and canine studies in 2010 and 2013, respectively, have shown that expression of HO-1 enzyme and inflammatory factors increased due to PM_{10} and diesel engine exhaust (DEE) exposure. Of the eight non-null epidemiological studies scrutinized, the majority included a retrospective study design with air pollution monitoring data, which may be an advantage due to large number of study participants and a disadvantage with possible air pollution measurement error for personal exposure. The studies included analyses of PM_{10}, $PM_{2.5}$, SO_2, NO_2, NO_x and/or O_3 with PM_{10} as the common denominator between all of them. Studies from 2003, 2014–2019 from Finland, France, Iran, Italy, and Serbia all provide evidence of an association between PM_{10} and incidence or relapse of MS. Though one 2018 study likewise described associations between exposures to NO_2, O_3, and PM_{10} and MS relapses using a case-crossover design, the multi-pollutant model only associated O_3. Of the epidemiological studies that fail to reject the null hypothesis, there was no evidence of an association between PM_{10} exposure and MS relapse or incidence. Though air pollution has not been conclusively proven to be a cause of MS, evidence from multiple studies have associated incidence and relapse with exposure to pollutants, particularly PM_{10}.

Key words: *air pollution, multiple sclerosis, relapse, particle matter, exposure, pollutants.*

The pathogenesis of multiple sclerosis (MS) is complex and the risk pattern contains both genetic and environmental components, as shown through extensive research over decades [1–3]. Several environmental factors can increase the risk of developing MS, such as Epstein Barr infection (EBV), smoking, low levels of vitamin D/sun exposure, and obesity. Many of these have been investigated in detail by the EnvIMS project (Environmental Risk Factors in MS) [4–9]. In addition, exposure to organic solvents has been investigated as a potential cause of MS [10]. In the EnvIMS studies, interestingly, a negative interaction between the risk of tobacco smoking and EBV infection was identified, indicating that there may be competing pathogenic pathways [5]. Recently, they also found a similar negative interaction regarding exposure to organic solvents versus EBV in-

Christina Zhukovsky – Graduate student at Department of Neuroscience (e-mail: christina.zhukovsky@neuro.uu.se; tel.: +46 18 611 000; ORCID: https://orcid.org/0000-0003-0934-4478).

Marie-Abèle Bind – ScD (e-mail: ma.bind@mail.harvard.edu; tel.: +1 (617) 495-5496; ORCID: https://orcid.org/0000-0002-0422-6651).

Inger Boström – PhD, Researcher, Division of Neurology, Department of Clinical and Experimental Medicine, Associate Professor (e-mail: inger.bostrom@liu.se; tel.: +46 13 281 000).

Anne-Marie Landtblom – Professor at Department of Neuroscience (e-mail: anne-marie.landtblom@neuro.uu.se; tel.: +46 07 055 91 670; ORCID: https://orcid.org/0000-0001-9567-470X).

fection as well as low vitamin D-level (low outdoor activity). Importantly, there seems to be a synergistic effect between organic solvent exposure and tobacco smoking [10–12]. Subsequently, inhaled chemical agents, like tobacco, obviously can trigger the inflammatory process in MS, and the focus of modern research should now turn to other common inhalations in man. Our interest, in the recent research in this field, has focused on air pollution and risks in MS, and presented as a review.

There have been multiple studies conducted all over the world with regard to the effects of air pollution on MS patients and though no consensus could be reached, there is much to say about the identified patterns. It is first important to note the source of air pollution. Avakian et al. [13] in 2002 noted that combustion processes are major emitters of NOx, SOx and byproducts which include particulate matter (PM) and metals. A 2005 study by Donaldson et al. [14] also noted that in an urban setting diesel engine exhaust emissions (DEE) are a major source of combustion-derived nanoparticles and ambient PM.

Mechanistic studies. Using animal studies in combination with human ones, one can see a pattern emerge. A 2003 study by Calderon-Garciduenas et al. [15] observed that canines exposed to PM had detectable quantities of PM-associated metals like Ni and V in the brain, expression of iNOS and COX2 as well as showed systemic inflammation. Additionally van Berlo et al. [16], like Calderon-Garciduenas et al. [15] noted associations between PM exposure and expression of enzymes like iNOS and COX-2. Van Berlo et al. [16] and Farina et al. [17] both showed through rat and mouse studies, respectively, that expression of Heme Oxygenase 1 (HO-1) enzyme and inflammatory factors increased due to PM_{10} and DEE exposure. In light of this, it is worthy to note that in 2001 Mehindate et al. [18] showed that MS spinal cord astroglia had a HO-1 overexpression, which may promote mitochondrial iron deposition in MS plaques.

With regards to humans, a 2004 study by Rose et al. [19] connected frequent COX-2 expression in association with iNOS in MS patients thereby suggesting the potential contribution to the pathology of MS through the involvement of these enzymes in inflammation. A limitation of this study included patient number.

Studies reporting positive associations. Most prevalent and reported environmental factor associated with MS relapse has been through the exposure to PM_{10}. An Iranian study from 2014 [20] looking at patients living within the area of the city of Tehran, observed significantly ($p < 0.001$) increased levels of PM_{10}, SO_2, NO_2 and NO_x but not NO as compared with controls. There, 2188 patients were geo-referenced and a cluster analysis performed using the average nearest neighbor index. The limitation of this study was that no additional confounder was considered in the analysis. Similarly, a French case-cross over designed study by Jeanjean et al. [21] with 424 MS patients, revealed that for MS relapses, within the scope of significant single-pollution exposures, there were associations due to NO_2, O_3 and PM_{10} levels. In a multi-pollutant model only O_3 remained significantly associated with occurrence of MS relapses. The strength of this study that single-pollutant and multi-pollutant conditional logistic regression models were used, stratified by season («hot» vs. «cold»), and adjusted for meteorological parameters and other factors [21]. A study by Angelici et al. [22] in 2016 that identified 8287 MS-related hospitalizations in the Lombardy region of Italy between 2001 and 2009, showed that hospital admission for MS increased by 42 % on the days preceded by one week with PM_{10} levels in the highest quartile. The limitations of this study were the lack of data on duration and effectiveness of the immunomodulatory therapy and ambient air pollution measurements for personal exposure. Nonetheless, this is in line with the findings of Oikonen et al. [23] (406 patients) and Roux et al. [24] (536 patients) both of which showed a correlation between the levels of PM_{10} and MS relapse. The former study was a retrospective one with data

collected from 1985–1999, while the latter collected from 2000–2009. A 2015 Serbian retrospective study by Vojinovic et al. [25] had results which confirmed the influence of seasonal changes in climate and air pollution on MS relapses. A limitation in this study was lack of blood samples from the MS patients. Bergamaschi et al. [26], using PM_{10} levels in the 5, 10, 15, 20, and 25 days before a brain MRI, also revealed a strong association between elevated PM_{10} levels and the risk of having an inflammatory lesion, independent of immune therapies, smoker status, and season.

Another recent study from 2019 by Tateo et al. [27] that included 1435 patients from the province of Padua, one of the most polluted geographical areas of Italy, revealed that MS prevalence was significantly higher ($p<0.0001$) in urban areas as compared with rural areas and had a strong correlation with the average annual concentrations of $PM_{2.5}$. The study showed that in the period 1998–2015, the annual levels of $PM_{2.5}$ were associated with the number of MS cases in urban areas and that the worst class of air quality was associated with the highest prevalence rate. A 2017 literature review by Mousavi et al. [28] likewise concluded that an association between air pollution and neurodegenerative diseases like MS exists. This was based on the similarity between mechanisms initiated due to MS and PM exposure.

Studies that failed to reject the null hypothesis. Several studies though have come to contradictory conclusions. A study by Palacios et al. [29] in 2017 did not show a significant association between air pollution and MS risk by using 2 large cohorts of US nurses, NHS and NHSII. In the second cohort, an elevation in risk of MS associated with exposure to PM_{10} was found but did not pass the test for trend across quantiles. Limitation wise, the NHS II study had younger participants and therefore showed a greater incidence of MS. Neither cohort showed any significant association between MS and exposure to $PM_{2.5}$. A 2018 study by Bai et al. [30] sought to investigate the association between MS incidence and exposure to $PM_{2.5}$, NO and O_3. 6203 cases were identified between 2001 and 2013 and after various sensitivity analyses as well as annual average temperature, they did not observe any significant associations between incidence and exposure. Some limitations of this study were that the exposure surfaces of $PM_{2.5}$, NO_2, and O_3 were derived at certain periods in time which possibly did not properly represent changes in the long-term in pollutant concentrations. Finally, a 2008 study by Tremlett et al. [31], which included 199 confirmed MS patients, was not able to associate ambient environmental factors such as PM_{10} and O_3 to MS relapses in Tasmania.

Conclusion. Although air pollution has not been directly proven to be a cause of MS, it has been suggested by multiple studies that there are associations between MS and air pollution, particularly PM10. Future in vitro and animal studies should further examine the biological mechanisms of the air pollution-MS relationship. Future human studies should examine the role of sex and epigenetic mechanisms (e.g., DNA methylation) in the air pollution-MS association, as well as study the potential interacting factors such as smoking and vitamin D deficiency. The key to understand the combined role of air pollution emissions is to reconstruct with observational data, hypothetical multi-factorial randomized experiments involving multiple pollutants, as argued by Pashley and Bind [32].

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