Association between rheumatic musculoskeletal diseases and air pollution: myth or reality?

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ABSTRACT

This review discusses the impact of air pollution exposure on rheumatic musculoskeletal diseases, and also considers air pollution assessment and its limitations. Rheumatic diseases are caused by dysregulation and excessive activation of the immune system, leading to systemic inflammation and immune-mediated damage. Air pollution, particularly particulate matter originating from fossil fuel combustion, increases the production of inflammatory cytokines and activates pathways involved in the inflammatory response. Long-term and short-term exposure to air pollution can be evaluated using various methodologies. Despite the limitations of exposure assessment, the review highlights the importance of monitoring air pollution levels to mitigate their harmful effects on human health and the environment.

KEYWORDS

Autoimmune diseases, rheumatic musculoskeletal diseases (RMDs), pollution, environment.

Introduction

Rheumatic diseases is a term that embraces a broad range of medical conditions that arise from dysregulation and excessive activation of the immune system, leading to systemic inflammation and immune-mediated damage [1]. The prevalence of these conditions has increased in recent years [1]. Although the exact cause of this increase remains unclear, it is widely believed that genetic predisposition and environmental factors play a significant role in the development of these diseases [2]. Among various environmental factors, air pollution has received considerable attention, partly due to the heightened awareness of its impact on public health. The primary components of air pollution are particulate matter (PM), a complex combination of chemical elements mostly originating from burning fossil fuels [3]. Many studies have shown that these substances increase the production of inflammatory cytokines (IL-1, IL-6, TNF) and activate various pathways involved in the inflammatory response [4,5]. Additionally, air pollution-induced inflammation in the lungs can contribute to the development of rheumatoid arthritis (RA) by directly citrullinating proteins; this triggers the release of anti-citrullination peptide antibodies [4,6,7].

In the present review we discuss the role of air pollution exposure (both acute and chronic) on rheumatic musculoskeletal diseases (RMDs). We also look at air pollution assessment and its limitations.

Assessing exposure to air pollution

In order to keep track of air pollution levels, one commonly used metric is PM [8]. PM is a complex mixture of solid particles suspended in the air; these particles, which have diameters ranging from < 0.1 microns to ≥ 100 microns, can come from a variety of sources, including fossil fuel combustion, dust, pollen, and other biological materials. PM is typically divided into two categories: coarse PM and fine PM. Coarse PM, also known as PM_{10}, is made up of particles with diameters of between 2.5 and 10 microns. These particles are often produced by mechanical processes such as crushing, grinding, and road traffic. Fine PM, on the other hand, includes particles with diameters smaller than 2.5 microns; for this reason, it is also known as $PM_{2.5}$. Fine PM is primarily produced by combustion sources such as motor vehicles and power plants, and it is considered particularly hazardous because these smaller particles can penetrate deep into the lungs and even enter the bloodstream, causing a range of respiratory and cardiovascular problems [9]. By monitoring levels of both coarse and fine PM, researchers can gain insight into the types of pollution present in a given area and take steps to mitigate their harmful effects on human health and the environment [10].

Investigation of the connection between air pollution exposure and health outcomes can be complicated by the numerous biases that can impact both exposure assessment and population selection in the research [11].

One way to monitor air quality is by means of stations spread across a particular area. Thousands of these air quality stations can be found in both Europe and the United States, and they are the most widely used approach for evaluating long-term

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and short-term exposure to air pollution. To link patient data to air quality data, zip code centroids are used, which can vary in size depending on the level of accuracy required. Nevertheless, this method may result in incorrect classification and may not accurately measure personal exposure [10]. Patients may change their location and commute to work, and the measurement of air quality may be affected by wet deposition, which refers to the removal of coarse PM from the atmosphere by rainfall [12].

Geospatial models that use satellite data to estimate PM on the Earth's surface may also be imprecise [13,14]. However, various strategies can be implemented to mitigate potential biases. For instance, questionnaires gathering information on personal exposure and commuting habits can be used to enhance exposure data. In addition, some models can now account for weather conditions, such as rainfall or wind.

Another way to assess exposure is through the use of personal monitors [11]. A range of devices is available, from expensive research-grade to more affordable commercial instruments. However, the majority of these monitors can only measure PM and may not be entirely accurate or precise. Despite these limitations, personal monitors are the most accurate approach for assessing personal exposure and can quantify both indoor and outdoor pollution [10]. Nonetheless, obtaining compliance from participants can be challenging, and studies might be limited by small sample sizes. Additionally, there may be a Hawthorne effect, where participants modify their behavior to reduce exposure to pollutants when wearing personal devices [15].

Assessing exposure to air pollution through direct measurement of certain toxins in biological samples, such as blood or urine, is the third and perhaps most complicated method. Benzene or benzopyrene, for instance, can be conveniently measured in frozen urine [16]. Although this method could potentially yield the most accurate estimate of personal exposure, it is subject to several limitations. First, it can only reflect cumulative exposure, and its duration is linked to the half-life of the target end-product being tested. In addition, there are inherent expenses, and conducting analyses requires research-grade facilities and laboratories.

Investigating chronic or acute exposure

Assessing the impact of air pollution on health outcomes can be complicated, as chronic and acute exposure need to be studied separately. To study the long-term effects of air pollution, it is necessary to use a methodology that can measure air quality over an extended period. The one most commonly used is air sampling through air quality stations, which provides an estimate of long-term exposure. However, the systematic measurement of airborne pollutants only began in the '80s–'90s, and estimating lifetime exposure to certain pollutants can be challenging. In most studies, long-term exposure is approximated from a specific time window, which may result in misclassification due to patient relocation or other factors. Acute exposure to high levels of air pollution can also be explored through the study of health-related events. Short-term exposures to air pollution can, for example, cause temporary changes in the risk of disease flares. A case-crossover study design is often used to investigate the effects on acute-onset diseases of transient exposure to a risk factor [17]. This methodology differs from traditional case-control studies as it compares two different periods of time within the same group of patients, who are followed longitudinally. This approach allows for better control of both between-patient and within-patient time-invariant confounders. The commonly used statistical tool in case-crossover studies is conditional logistic regression, which helps control for time-varying confounders such as changes in medication or infections [18].

Air pollution and rheumatic musculoskeletal diseases (RMDs)

In the last decade a variety of observational studies (both cross-sectional and longitudinal) have provided empirical evidence on the association between air pollution and autoimmune diseases. This association was demonstrated in numerous conditions, including RA, systemic lupus erythematosus, multiple sclerosis, and other inflammatory and non-inflammatory diseases [19-32]. In a recent observational study, a small but significant correlation was found between exposure to $PM_{2.5}$ and the risk of being diagnosed with an autoimmune disease [30]. Specifically, for every 10 μg/m^3 increase in $PM_{2.5}$ concentration, the risk of having any autoimmune disease increased by 7%. The study also found that chronic exposure to both PM_{10} (>30 μg/m^3) and $PM_{2.5}$ (>20 μg/m^3) increases the risk of autoimmune diseases. It is important to note that while the increase in risk associated with PM10 exposure is small, it could have significant public health implications given the widespread exposure to air pollution in many parts of the world. The prevalence of RA was nearly 50% higher in subjects exposed to high levels of PM.

Recent studies have found a correlation between exposure to PM and reactivations of RA, eventually leading to a change in treatment [27,28]. The findings of the studies indicated a higher risk of altered C-reactive protein (CRP) levels with increased exposure to PM_{10}. Specifically, a 150% and 65% higher risk of having CRP greater than 5 mg/L was observed in the presence of PM_{10} exposures of more than 50 μg/m^3 and 40 μg/m^3, respectively. Even when the PM_{10} exposure threshold was set at 30 μg/m^3 (below the European Union health protection limit), a 38% higher risk of altered CRP levels was observed. The study also found that air pollutant concentrations were higher before a drug switch or swap due to drug inefficacy. Therefore, air pollution is a modifiable environmental factor linked to the pathogenesis of chronic inflammatory arthritis. This is especially true for RA, as the substances found in air pollutants are largely the same toxic components present in cigarette smoke. However, the biological rationale for the poor treatment response observed in patients with RA makes this association highly probable for other forms of chronic inflammatory arthritis as well. Air pollutant concentrations were higher in the 1-2 months leading up to an arthritic flare. Exposure to air pollution has indeed been suggested to be a pro-inflammatory stimulus, which increases the risk of chronic inflammatory arthritides and other pathologies.

Consistent with this theory, the 60-day period may provide a more accurate reflection of the cumulative exposure burden.

Interestingly, Bellinato *et al*. conducted a retrospective study and discovered that air pollution is associated with exacerbations not only of rheumatological diseases, but also dermatological conditions [31,32]. The authors found that all types of pollutants were significantly more concentrated in the 60 days before a psoriasis flare than in the 60 days before the control visit. Exposure to mean PM_{10} levels of over 20 μg/m^3 and mean $PM_{2.5}$ levels of over 15 μg/m^3 in the 60 days prior to assessment was associated with a higher risk of a 5-point or greater worsening of the Psoriasis Area and Severity Index. This association was also found in patients with atopic dermatitis.

Studies have shown that exposure to PM can have a negative impact on bone health by promoting the secretion of RANKL and, therefore, altering the RANKL to osteoprotegerin ratio [33,34]. This effect appears to be mediated by increased secretion of RANKL induced by inflammatory cytokines. RANKL is a cytokine that plays a key role in bone remodeling, and its overproduction can lead to bone loss and osteoporosis. Furthermore, exposure to high concentrations of PM in the lower atmosphere can also have a negative impact on vitamin D production [35]. This is because high levels of PM can reduce the amount of UVB radiation — necessary for the skin to produce vitamin D — that reaches the Earth's surface. Vitamin D is essential for maintaining bone health, as it helps the body absorb calcium and phosphorus. A deficiency in vitamin D can increase the risk of bone diseases such as osteoporosis and fractures. In turn, there is a strong rationale for the association between air pollution and osteoporosis, which has indeed been demonstrated in clinical studies [29,36,37]. According to several population-based cohort studies, exposure to air pollution can lead to a reduction in bone mineral density levels [29,38-41]. Interestingly, cortical sites were more vulnerable to the harmful effects of PM exposure than trabecular sites. Additionally, t-scores were more negatively impacted by $PM_{2.5}$ than by PM_{10} exposure. Overall, prolonged exposure to high levels of atmospheric pollutants may increase the risk of developing osteoporosis by as much as 15%.

Due to the known association between air pollution and osteoporosis, researchers have also looked into a potential link between acute exposure to atmospheric pollutants and the risk of hip fractures [42,43]. An intriguing case-crossover study found that exposure to air pollution was higher in the 30 and 60 days leading up to a fracture as compared to a control period before the hazard period. The study showed that the risk of fracture increased as the concentration of PM_{10} did, with an incremental risk of 7.7% for every 10 μg/m^3 increase in PM_{10}. Individuals over the age of 85 were found to be at higher risk, with an 11.6% increase in fracture risk for the same increase in PM_{10} concentration. Similarly, individuals over the age of 80 had a 10.5% increase in risk, while those under 85 years of age had a 6.2% and those under 80 years a 1.0%. To summarize, it can be concluded that the elderly population is more vulnerable to the adverse impacts of short-term exposure to air pollution.

In general, it can be said that components of air pollution (both gaseous and particulate) can exert negative effects on the immune system, and that these effects can seemingly be either permanent or transitory [2].

Even though there is no clear and defined association between specific air pollution components and their effects, it is interesting to note that high NO_2 exposure was more deleterious than PM_{10} exposure [27,28]. It has been observed that exposure to high ambient air pollutants, including $PM_{2.5}$, NO_2, and NOx, was significantly associated with an increase in osteoporosis risk [44]. The effects of single air pollutants, such as NO_2 and $PM_{2.5}$, on health have been widely demonstrated. However, given that humans are exposed to a mixture of air pollutants, it is important to try and use a mixture of pollutant exposure estimation methods [45]. These considerations suggest that certain pollutants might be more specifically involved in the alterations mentioned. Additional studies comparing the different components of air pollution and their effects would be useful.

Conclusions

Air pollution and climate change are significant challenges that pose health and societal risks [46]. The World Health Organization reports that over 7 million deaths occur each year due to the effects of air pollution, and that most of these fatalities could have been prevented by reducing fossil combustion emissions [9]. The environment has a crucial role in the pathogenesis of RMDs [2]. Studies have shown that exposure to air pollution increases the risk of autoimmune diseases, including RMDs. Short-term exposure to high levels of airborne pollutants can also lead to flares in RMDs. While the mechanisms by which air pollution contributes to the development of autoimmune diseases are not entirely understood, it is believed that pro-inflammatory cytokines, oxidative stress, and changes in immune cell function play a role.

Although recent research has made strides in understanding the link between air pollution and autoimmune diseases, much work remains to be done. Future studies should focus on characterizing the effects of specific air pollutants and their mixtures on the immune system, identifying individual and environmental factors that influence susceptibility, and examining the effectiveness of interventions such as air pollution control measures and lifestyle changes in reducing the risk of autoimmune diseases in people exposed to air pollution.

References

1. Rose NR. Prediction and prevention of autoimmune disease in the 21st century: a review and preview. Am J Epidemiol. 2016;183(5):403-6.
2. Adami G. Mining the pathogenesis of rheumatoid arthritis, the leading role of the environment. RMD Open. 2022;8(2):e002807.
3. Brunekreef B, Holgate ST. Air pollution and health. Lancet. 2002; 360(9341):1233-42.
4. Colasanti T, Fiorito S, Alessandri C, et al. Diesel exhaust particles induce autophagy and citrullination innormal human bronchial epithelial cells. Cell Death Dis. 2018;9(11):1073.
5. Pope CA 3rd, Bhatnagar A, McCracken JP, Abplanalp W, Conklin DJ, O'Toole T. Exposure to fine particulate air pollution is associated with endothelial Injury and systemic inflammation. Circ Res. 2016;119(11):1204-14.

6. Valesini G, Gerardi MC, Iannuccelli C, Pacucci VA, Pendolino M, Shoenfeld Y. Citrullination and autoimmunity. Autoimmun Rev. 2015;14(6):490-7.
7. Perricone C, Versini M, Ben-Ami D, et al. Smoke and autoimmunity: the fire behind the disease Autoimmun Rev. 2016;15(4):354-74.
8. Han B, Hu LW, Bai Z. Human exposure assessment for air pollution. Adv Exp Med Biol. 2017;1017:27-57.
9. WHO. Ambient (outdoor) air pollution. 19 December 2022. Available at: https://www.who.int/news-room/fact-sheets/detail/ambient-(outdoor)-air-quality-and-health. Accessed January 28, 2023.
10. Dias D, Tchepel O. Spatial and temporal dynamics in air pollution exposure assessment. Int J Environ Res Public Health. 2018;15(3):558.
11. Hassan Bhat T, Jiawen G, Farzaneh H. Air Pollution Health Risk Assessment (AP-HRA), Principles and Applications. Int J Environ Res Public Health. 2021;18(4):1935.
12. Yang T, Wang Y, Wu Y, et al. Effect of the wetland environment on particulate matter and dry deposition. Environ Technol. 2020;41(8):1054-64.
13. Stafoggia M, Bellander T, Bucci S, et al. Estimation of daily PM10 and PM2.5 concentrations in Italy, 2013-2015, using a spatiotemporal land-use random-forest model. Environ Int. 2019;124:170-9.
14. Fioravanti G, Martino S, Cameletti M, Cattani G. Spatio-temporal modelling of PM10 daily concentrations in Italy using the SPDE approach. Atmospheric Environment. 2021;248:118192.
15. Sedgwick P, Greenwood N. Understanding the Hawthorne effect. BMJ. 2015;351:h4672.
16. Weisel CP. Benzene exposure: an overview of monitoring methods and their findings. Chem Biol Interact. 2010;184(1-2):58-66.
17. Maclure M. The case-crossover design: a method for studying transient effects on the risk of acute events. Am J Epidemiol. 1991;133(2):144-53.
18. Consiglio GP, Burden AM, Maclure M, McCarthy L, Cadarette SM. Case-crossover study design in pharmacoepidemiology: systematic review and recommendations. Pharmacoepidemiol Drug Saf. 2013; 22(11):1146-53.
19. Bernatsky S, Smargiassi A, Joseph L, et al. Industrial air emissions, and proximity to major industrial emitters, are associated with anti-citrullinated protein antibodies. Environ Res. 2017;157:60-63.
20. Bernatsky S, Smargiassi A, Barnabe C, et al. Fine particulate air pollution and systemic autoimmune rheumatic disease in two Canadian provinces. Environ Res. 2016;146:85-91.
21. Cooper GS, Wither J, Bernatsky S, et al. Occupational and environmental exposures and risk of systemic lupus erythematosus: silica, sunlight, solvents. Rheumatology (Oxford). 2010;49(11):2172-80.
22. Liu JL, Woo JMP, Parks CG, Costenbader KH, Jacobsen S, Bernatsky S. Systemic lupus erythematosus risk: the role of environmental factors. Rheum Dis Clin North Am. 2022;48(4):827-43.
23. Liu Q, Gu X, Deng F, et al. Ambient particulate air pollution and circulating C-reactive protein level: asystematic review and meta-analysis. Int J Hyg Environ Health. 2019;222(5):756-64.
24. Jung CR, Chung WT, Chen WT, Lee RY, Hwang BF. Long-term exposure to traffic-related air pollution and systemic lupus erythematosus in Taiwan: a cohort study. Sci Total Environ. 2019;668:342-9.
25. Zhao N, Smargiassi A, Hatzopoulou M, et al. Long-term exposure to a mixture of industrial SO2, NO2, and PM2.5 and anti-citrullinated protein antibody positivity. Environ Health. 2020;19(1):86.
26. Zhao N, Smargiassi A, Hudson M, Fritzler MJ, Bernatsky S. Investigating associations between anti-nuclear antibody positivity and combined long-term exposures to NO2, O3, and PM2.5 using a Bayesian kernel machine regression approach. Environ Int. 2020;136:105472.
27. Adami G, Viapiana O, Rossini M, et al. Association between environmental air pollution and rheumatoid arthritis flares. Rheumatology (Oxford). 2021;60(10):4591-7.
28. Adami G, Rossini M, Viapiana O, et al. Environmental air pollution is a predictor of poor response to biological drugs in chronic inflammatory arthritides. ACR Open Rheumatol. 2021;3(7):451-6.
29. Adami G, Cattani G, Rossini M, et al. Association between exposure to fine particulate matter and osteoporosis: a population-based cohort study. Osteoporos Int. 2022;33(1):169-76.
30. Adami G, Pontalti M, Cattani G, et al. Association between long-term exposure to air pollution and immune-mediated diseases: a population-based cohort study. RMD Open. 2022;8(1):e00205.
31. Bellinato F, Adami G, Vaienti S, et al. Association between short-term exposure to environmental air pollution and psoriasis flare. JAMA Dermatol. 2022;158(4):375-81.
32. Bellinato F, Adami G, Furci A, et al. Association between short-term exposure to environmental air pollution and atopic dermatitis flare in patients treated with dupilumab JAAD Int. 2023;11:72-7.
33. Saha H, Mukherjee B, Bindhani B, Ray MR. Changes in RANKL and osteoprotegerin expression after chronic exposure to indoor air pollution as a result of cooking with biomass fuel. J Appl Toxicol. 2016;36(7):969-76.
34. Prada D, López G, Solleiro-Villavicencio H, Garcia-Cuellar C, Baccarelli AA. Molecular and cellular mechanisms linking air pollution and bone damage. Environ Res. 2020;185:109465.
35. Rahman A, Elmi A. Air pollutants are negatively associated with vitamin D-synthesizing UVB radiation intensity on the ground. Sci Rep. 2021;11(1):21480.
36. Nguyen TV. Air pollution: a largely neglected risk factor for osteoporosis. Lancet Planet Health. 2017;1(8):e311-e312.
37. Ryu HJ, Seo MR, Choi HJ, Cho J, Baek HJ. Particulate matter (PM10) as a newly identified environmental risk factor for acute gout flares: a time-series study. Joint Bone Spine. 2021;88(2):105108.
38. Zhang F, Zhou F, Liu H, et al. Long-term exposure to air pollution might decrease bone mineral density T-score and increase the prevalence of osteoporosis in Hubei province: evidence from China Osteoporosis Prevalence Study. Osteoporos Int. 2022;33(11):2357-68.
39. Prada D, Crandall CJ, Kupsco A, et al. Air pollution and decreased bone mineral density among Women's Health Initiative participants. EClinicalMedicine. 2023;57:101864.
40. Mousavibaygei SR, Bisadi A, ZareSakhvidi F. Outdoor air pollution exposure, bone mineral density, osteoporosis, and osteoporotic fractures: a systematic review and meta-analysis. Sci Total Environ. 2023;865:161117.
41. Ranzani OT, Milà C, Kulkarni B, Kinra S, Tonne C. Association of ambient and household air pollution with bone mineral content among adults in peri-urban South India. JAMA Netw Open. 2020;3(1):e1918504.
42. Adami G, Olivi P, Pontalti M, et al. Association between acute exposure to environmental air pollution and fragility hip fractures. Bone. 2023;167:116619.
43. Mazzucchelli R, Crespi Villarias N, Perez Fernandez E, et al. Short-term association between outdoor air pollution and osteoporotic hip fracture. Osteoporos Int. 2018;29(10):2231-41.
44. Xu C, Weng Z, Liu Q, et al. Association of air pollutants and osteoporosis risk: the modifying effect of genetic predisposition. Environ Int. 2022;170:107562.
45. Zhang J, Fang XY, Wu J, et al. Association of combined exposure to ambient air pollutants, genetic risk, and incident rheumatoid arthritis: a prospective cohort study in the UK Biobank. Environ Health Perspect. 2023;131(3):37008.
46. Stafoggia M, Oftedal B, Chen J, et al. Long-term exposure to low ambient air pollution concentrations and mortality among 28 million people: results from seven large European cohorts within the ELAPSE project. Lancet Planet Health. 2022;6(1):e9-e18.

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