Rheumatoid Arthritis Activity and Short-Term Exposure to Air Pollutants in Metropolitan Areas in the North of Italy

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November 9, 2020

Abstract

Background. Rheumatoid arthritis (RA) flare is related to an increased joint damage, disability and healthcare use. The impact of short-term air pollution exposure on RA activity is still a matter of debate. We investigated in a cross-sectional study whether short-term exposure to particulate matter (PM)10, PM2.5, nitrogen dioxide (NO2) and ozone (O3) affected RA disease activity. Methods. 422 consecutive RA patients resident in Lombardy, North of Italy were studied. Air pollutant concentrations, estimated by Regional Environmental Protection Agency (Lombardy – Italy) at municipality resolution, were used to assign short-term exposure from the day of visit back to 14 days. Results. Sparse punctual significant negative associations emerged between PM10, PM2.5, NO2 and RA disease activity, whereas positive associations were observed for O3. Moreover, patients were stratified according to their ongoing Disease Modifying anti-Rheumatic Drugs (DMARDs) treatment: no DMARDs (n=25), conventional synthetic - csDMARDs (n=108), and biological or targeted synthetic b/tsDMARDs (n=289). At visit, an inverse association was observed in the b/tsDMARDs group between PM2.5 and Disease Activity Score on 28 joints (DAS28) (-0.047±0.020, p=0.023), a positive tendency in the no-DMARD group (0.125±0.070, p=0.075) and no association for csDMARDs group (0.042±0.039, p=0.288). The association between O3 the day before the visit and DAS28 was positive only in the b/tsDMARDs group (0.038±0.009, p<0.001). Conclusion. The impact of air pollution short-term exposure seems minimally clinical relevant, as the scattered significant differences were observed. Further evidence is needed to elucidate determinants of RA flare and the implications for management.

Running Title: Rheumatoid arthritis and short-term pollutants exposure

RHEUMATOID ARTHRITIS ACTIVITY AND SHORT-TERM EXPOSURE TO AIR POLLUTANTS IN METROPOLITAN AREAS IN THE NORTH OF ITALY

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ABSTRACT

Background. Rheumatoid arthritis (RA) flare is related to an increased joint damage, disability and healthcare use. The impact of short-term air pollution exposure on RA activity is still a matter of debate. We investigated in a cross-sectional study whether short-term exposure to particulate matter $(PM)_{10}$, $PM_{2.5}$, nitrogen dioxide (NO_2) and ozone (O_3) affected RA disease activity.

Methods. 422 consecutive RA patients resident in Lombardy, North of Italy were studied. Air pollutant concentrations, estimated by Regional Environmental Protection Agency (Lombardy – Italy) at municipality resolution, were used to assign short-term exposure from the day of visit back to 14 days.

Results . Sparse punctual significant negative associations emerged between PM_{10}, $PM_{2.5}$, NO_2 and RA disease activity, whereas positive associations were observed for O_3. Moreover, patients were stratified according to their ongoing Disease Modifying anti-Rheumatic Drugs (DMARDs) treatment: no DMARDs (n=25), conventional synthetic - csDMARDs (n=108), and biological or targeted synthetic b/tsDMARDs (n=289). At visit, an inverse association was observed in the b/tsDMARDs group between $PM_{2.5}$ and Disease Activity Score on 28 joints (DAS28) (-0.047±0.020, p =0.023), a positive tendency in the no-DMARD group (0.125±0.070, p =0.075) and no association for csDMARDs group (0.042±0.039, p =0.288). The association between O_3 the day before the visit and DAS28 was positive only in the b/tsDMARDs group (0.038±0.009,p <0.001).

Conclusion. The impact of air pollution short-term exposure seems minimally clinical relevant, as the scattered significant differences were observed. Further evidence is needed to elucidate determinants of RA flare and the implications for management.

What's already known about this topic?

- Long-term environmental exposures may promote the onset of rheumatoid arthritis (RA).

- RA flares spanning disease course are related to an increased disability and healthcare use.

What does this article add?

Short-term (14 days) air pollutants exposure seems minimally clinically relevant.

Different therapies could potentially influence the link between disease activity and air pollution.

Keywords : rheumatoid arthritis; air pollution; particulate matter; disease activity

Funding details: No specific funding was received from any bodies in the public, commercial or not-for-profit sectors to carry out the work described in this article.

Disclosure statement: The authors declare no conflicts of interest

Data availability statement : data of the Regional Environmental Protection Agency are available at www.arpalombardia.it/Pages/Aria/Modellistica/I-sistemi-modellistici-in-ARPA.aspx

Introduction

Rheumatoid arthritis (RA), mainly characterized by inflammatory joint involvement potentially leading to a progressive disability; it is considered a global public health challenge with almost 20 million prevalent cases, 1.2 million incident cases and 3.4 million disability-adjusted life years [1]. Despite our considerable knowledge of heterogeneous clinical phenotypes of RA, both genetic and environmental factors underpinning RA are not fully understood.

Specifically, it has been shown that environmental exposures (e.g. cigarette smoking, silica dust and mineral oil) may promote oxidative stress that causes bronchial and systemic inflammation, which, in turn, enhances monocytes and dendritic cells to present auto-antigens and to favour anti-citrullinated protein antibodies (ACPA) production in inducible bronchus-associated lymphoid tissue [2-6]. Thus, a failure to maintain homeostatic host-environment interactions along the lung mucosal border has been proposed as a key factor in the multifactorial pathogenesis of RA.

The role of long-term exposure to air pollution in RA development was investigated in several studies, with controversial results [7-12]. An increased risk of RA (about 30%) was found in women living within 50 meters from a trafficked road compared to women living further [7]. Similarly, in a large population-based Canadian study, RA risk was incremented for people living closer to a highway, even if exposure to specific pollutants was not found accountable [8]. A positive association was also found between particulate matter $(PM)_{2.5}/NO_2$ levels and the risk of developing a systemic autoimmune rheumatic disease in two different Canadian studies [9, 10]. Conversely, other studies failed to find an association between air pollution and RA susceptibility [11, 12]. A very recent metanalysis reported that long-term exposure to O_3 and living near traffic roads could increase the risk of RA, while other pollutants, such as PM, didn't seem to have an impact [13].

In addition, advances in the understanding of the potential triggers of RA flares during the disease course are also important for different reasons: to complement and improve RA management, to give the opportunity to devise preventative strategies, and to avoid disease relapse or gradual loss of drug responsiveness that substantially contributes to patient poorer health-related quality of life, disability, healthcare use and costs [14]. To date, only two studies have been published on this topic. The first is based on the Kuwait Registry for Rheumatic Diseases, describing the detrimental effects of short-term SO_2 and NO_2 exposure on RA disease activity, while no correlation was found for PM_{10}, O_3 and CO [15]. The second study provides evidence that exposure to high concentration of $PM_{2.5}$ and NO_2 was related to hospital readmission of RA patients within one year after the last discharge in Hefei (China) [16].

In the present study, we aimed to investigate whether short-term exposure (14 days) to air pollutants (PM_{10}, $PM_{2.5}$, NO_2 and O_3) influence disease activity indices in RA patients referring to an Academic Rheumatology Unit in Milan, North of Italy.

Materials and methods

Study design

This is a cross-sectional, single-centre, no-profit study. Between January and June 2018, all consecutive adult RA patients according to the American College of Rheumatology (ACR) and/or 2010 ACR/European League Against Rheumatism classification criteria [17, 18], resident in Lombardy (North of Italy) with disease duration [?] 3 months who referred to the out-patient rheumatology clinics of the Division of Clinical Rheumatology (Pini Hospital, University of Milan, Italy) were enrolled. The local ethics committee "Comitato Etico Milano Area 2" approved this study (approval code 17_2018). An informed written consent was obtained from all subjects. All patients with overlap syndromes were excluded. Demographic and clinical data, disease activity (tender and swollen joint count -TJC and SJC, DAS28-CRP - Disease Activity Score in 28 joints with C-Reactive Protein and SDAI - Simplified Disease Activity Index), ongoing treatment, patient's Global Health (GH), Physician's and Patient's disease activity Global Assessments (PhGA, PaGA) were collected.

Exposure assessment

Daily mean PM_{10}, $PM_{2.5}$, NO_2 and O_3 concentrations derive from the archives of the Regional Environmental Protection Agency (ARPA Lombardia) that collects results of the simulations, on a regional scale, of the FARM (Flexible Air quality Regional Model) chemical-physical model of air quality [19], a three-dimensional Eulerian model simulating dispersion and chemical reactions of atmospheric pollutants available at municipality resolution (www.arpalombardia.it/Pages/Aria/Modellistica/I-sistemi-modellistici-in-ARPA.aspx). A variability in exposures between subjects exists due to spatial and temporal variability, as each patient was assigned the daily concentration of all pollutants at the municipality in which they live, the day of evaluation and back to 14 days (i.e. from day 0 to day -14) and the mean of one week before enrolment (*i.e.* week-1 is the mean of the day 0-to day-7). Only patients from the Lombardy region (located in the north of Italy) were considered for the study.

Statistical analysis

Classic descriptive statistical methods were used to evaluate the distribution of continuous and categorical variables. Multivariable linear regression models were performed to identify the day of PM_{10}, $PM_{2.5}$, NO_2 and O_3 independently associated with DAS28, SDAI, GH, PhGA, PaGA, TJC and SJC, adjusting for radiological damage, smoking habits (three categories), seropositivity for rheumatoid factor and/or ACPA (yes/no), therapy with Disease Modifying anti-Rheumatic Drugs (DMARDs) (no DMARDs, conventional synthetic - csDMARDs, targeted synthetic - tsDMARDs, biological - bDMARDs), use of steroids, age at examination, and disease duration. The potential effect modification of the therapy was investigated adding an interaction term between pollutants and therapy in each model. When the interaction term resulted significant (p <0.05), the association between pollutant and outcome was investigated in each subgroup of therapy. β coefficients were reported for 10 $\mu g/m^3$ increments of PM_{10}, $PM_{2.5}$, O_3 and NO_2 concentrations. As the distribution of the outcome variables (DAS28, SDAI, GH, PhGA, PaGA, TJC and SJC) were skewed, they were log-transformed. All statistical analyses were performed using SAS 9.4 (SAS Institute, Cary, NC, USA). The data underlying this article will be shared on reasonable request to the corresponding author.

Results

Patient characteristics and exposure assessment

A total of 422 consecutive RA patients were enrolled; mean age was 58.2 years and mean disease duration was 16.1 years. The other demographic data and disease characteristics are reported in Table 1. RA patients were stratified in three subgroups according to their ongoing treatment: 1) 25 subjects without an ongoing DMARDs (*e.g.* drug washout for side effects or comorbidities, long-standing remission, or programmed therapy switch); 2) 108 treated with csDMARDs; 3) 289 patients treated with b/tsDMARDs. Based on the

main demographic and clinical characteristics, the three groups were similar, except for smoking habits and positivity for RF and/or ACPA that were higher in the b/tsDMARDs group. Disease activity indexes were similar in the 3 groups, except for PhGA (p=0.05) and TJC (p=0.036) that were higher in patients with no therapy.

Daily concentrations of PM_{10}, $PM_{2.5}$, O_3 and NO_2 at patients' municipality are reported in Supplementary Table S1-S4. A map representation of the four pollutants is reported in figure 1. Each map reports the mean value, over the entire study period, for each municipality, and the subjects of the study georeferenced to their residential address.

Association between air pollutants and RA disease activity

Regarding the association between $PM_{2.5}$ and RA disease activity (DAS28 and SDAI), no statistically significant changes, in the week preceding the visit, were observed in the multivariable linear regression models (Table 2). PaGA, PhGA and TJC showed statistically significant association with $PM_{2.5}$ only for some scattered days before the evaluation (Supplementary Table S5).

When therapy was studied, a significant interaction was found for $PM_{2.5}$ at the day of the visit, resulting in an inverse association between $PM_{2.5}$ and DAS28 for patients with b/tsDMARD and no significant association for patients untreated and treated with csDMARDs (Supplementary Figure S1).

Considering the association between PM_{10} and RA disease activity, a statistically significant change 5 days before the visit was observed (p=0.034) (Table 2). PhGA and TJC showed scattered statistically significant associations with PM_{10}(Supplementary Table S6). The association between $PM_{10}$and RA disease activity was not modified by therapy.

Association between NO_2 and RA disease activity was significant at the day of the visit and at the day before (Table 3). PhGA showed a statistically significant association with NO_2 the day before the visit and two days before (Supplementary Table S7). The association between $NO_2$and RA disease activity was not modified by therapy.

O_3 displayed an opposite trend, a statistically significant association was observed with DAS28, SDAI, GH and PhGA for exposures experienced the day preceding the visit, and five days before for DAS28 and PhGA. Interaction of O_3 with therapy was particularly evident in several days before the visit (Table 3, Supplementary Table S8 and Figure S2).

Since there were no significant differences between the first and the second week before the evaluation, we reported only results referring to 7 days before the visit for all the pollutants considered.

Discussion

Disease activity in our Italian cohort of RA patients was not significantly affected by short-term air pollutants exposure in urban and peri-urban areas in Lombardy region in the North of Italy. Notably, scattered statistical significant associations were observed between short-term exposure to outdoor air pollutants (PM_{10}, $PM_{2.5}$, NO_2, and O_3) and RA activity, but the changes observed did not reach the minimal clinically important difference [20].

A clear comparison with the purpose of establishing whether a difference exists between our results and the two existing studies on this topic is not feasible [15, 16]. Firstly, our RA population includes all consecutive patients referring to the Rheumatology outpatient clinics and the disease activity was low between remission and low disease activity (see table 1). By contrast, in the study of Wu, hospital re-admissions within one year were considered, thus suggesting more severe flares of disease [16], while the Kuwaiti Colleagues described an association between DAS28, clinical disease activity index (CDAI), NO_2 and SO_2 using data from their national registry [15]. This latter study, as well as our results, provided very small variations in outcome measure (i.e. disease activity), which, even if statistically significant, did not reach the minimal clinically important difference [20].

Furthermore, accurate measurement of the household and workplace air pollution was not included in all these studies. These findings are consistent with studies on cigarette smoking exposure that is recognized as one of the most influencing environmental factors for RA susceptibility, but there is no evidence of its influence in a very short time on disease activity [21]. Moreover, our results are in line with those on systemic lupus erythematosus disease activity and short-term air pollution exposure [22].

Notably, strength of our study was to consider different therapeutic approaches as a potential confounding factor. Therapy seems partially able to influence the relationship between short-term air pollution exposure and RA disease activity. It should be noted that this result is limited to $PM_{2.5}$ levels and DAS28 at the day of the visit and O_3 levels and disease activity scores (DAS28 and SDAI) for several days with respect to the three groups of therapies.

Some limitations of our study have to be mentioned. This is a single center study and data are limited to our tertiary referral center. In addition, we could not measure all real life exposures, even those related to daily activities that can also affect results.

As already mentioned, much of our current understanding of the impact of air pollution on RA pathobiological events has been derived from long-term retrospective studies using registries or administrative databases or in vitro studies [4, 5, 13]. Although the environment seems to play a crucial role in inducing autoimmunity by favouring disease onset, it seems barely relevant to disease activity once the loss of tolerance is established in rheumatologic disorders.

In conclusion, despite the strong in vitro evidence that particulate matter enhances the inflammatory pathways, the evidence of this effect in real-life RA patients is less impressive. The role of short-term exposure to air pollutants as a potential contextual factor has not yet clarified. Further research shall help further elucidate determinants of RA flare and the implications for disease management.

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Tables and Figures Legends

Table 1. Demographic and disease patient characteristics.

Table 2. Associations between $PM_{2.5}$ and PM_{10} short-term exposure and RA disease activity.

Table 3. Associations between NO_2 and O_3 short-term exposure and RA disease activity.

Figure 1. Graphical representation of PM_{10}, $PM_{2.5}$, NO_2, and O_3concentration levels.

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