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Influence of Air Pollutants on the Disease Activity and Quality of Life in Rheumatoid Arthritis, an Iranian Observational Longitudinal Study

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Abstract

Background: Environmental exposures and genetic predisposition interactions may result in autoimmune rheumatic diseases. This study aimed to determine the effect of outdoor air pollutants on the activity of rheumatoid arthritis (RA) in a longitudinal follow-up.

Methods: We longitudinally studied 50 patients with RA bimonthly over 6 months in Mashhad, one of the most polluted cities in Iran. Disease activity and health-related quality of life (HRQoL) were examined according to the disease activity score (DAS28ESR), health assessment questionnaires (HAQ), physical health component summary (PCS), and visual analogue scale (VAS) criteria. The outdoor air pollutant was measured by monitoring the average concentration of nitrogen oxide (NO), carbon monoxide (CO), O_2 level, Sulfur dioxide (SO_2), and some particles less than 10 and 2.5 micrometers in diameter (PM <10 µm, PM <2.5 µm). The temperature and humidity levels were also measured. The univariate and multivariate statistical analyses were used for data analysis and the role of confounding factors was determined using the generalized estimation equation method.

Results: Statistical analysis indicated a significant increase of the DAS28ESR (B = 0.04 [0.08]; $P = 0.01$) and VAS (B = 4.48 [1.73]; $P = 0.01$) by CO concentration. Moreover, a number of polluted days increased the VAS in patients. In addition, other air pollutants, temperature, and humidity were not affected significantly by the DAS28ESR and quality of life indexes by considering confounders such as medications, age, and job.

Conclusion: Based on our findings, CO concentration was the only effective outdoor air pollutant that could increase RA disease activity. In addition, CO concentration and the number of polluted days make patients feel more ill. As the role of indoor air pollutants is highly important, further research on this critical topic is required to establish the role of air pollution on RA disease activity.

Keywords: Rheumatoid Arthritis, Disease Activity, Carbon Monoxide, Air Pollution, Nitric Oxide, Temperature, Humidity, PM <10 µm, PM <2.5 µm

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Introduction

Rheumatoid arthritis (RA) is a systemic, autoimmune, chronic, inflammatory disease that targets joints and cartilages, leading to progressive joint erosions and severe disability. RA is evaluated to affect approximately 0.2% of the worldwide population while using disability-adjusted life years represented an increase from 3,335,000 to 4,815,000 between 1990 and 2010 (1-3). Autoimmune diseases are a wide range of disorders manifested by the body's immune

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↑What is "already known" in this topic:
Environmental exposures and genetic predisposition interactions may result in autoimmune rheumatic diseases. Several studies revealed that the morbidity and mortality rate, predominantly in respiratory and cardiovascular systems are conventionally influenced by air pollutants in autoimmune diseases such as rheumatoid arthritis (RA).

→What this article adds:
This study determined the increased effect of air pollutants on disease activity and quality of life in RA patients in Mashhad, Iran, in 2018. Our data analysis indicated a significant negative influence of CO concentration on the VAS and DAS28ESR.

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responses to its tissues, leading to chronic inflammation and additional tissue damage. Lately, air pollution exposure has resulted in the extension of autoimmune diseases (4).

Environmental exposures and genetic predisposition interaction may bring about several autoimmune rheumatic diseases, such as RA (1, 5). Furthermore, it is represented only in 1 study that particulate matter with aerodynamic diameter ≤ 2.5 μm (PM2.5) exposure might be associated with an increased risk of systemic autoimmune diseases (6). Several studies have suggested that environmental factors such as air pollution are associated with autoimmune diseases. In this regard, the effects of traffic-inhaled pollutants as the primary source of air pollution, smoking, ozone, silica, dioxin, and noise on RA were investigated (2, 5, 7). A nationwide retrospective cohort study showed that exposure to nitrogen dioxide (NO) pollution increased the risk of RA, and regardless of adjustment for potential confounding factors, this significant association remained stable (2).

Meanwhile, a Canadian nested case-control study reported an increased risk of RA with ozone exposure (8). Another case-control study has illustrated that the risk of RA notably grew with the concentrations of NO and sulfur dioxide (SO_2) (9). These effects were demonstrated in short- and long-term air pollution studies, resulting in significant adverse public health effects and losing millions of dollars each year (3). The Nurses' Health Study (NHS) cohort in the United States has demonstrated that people living within 50 meters of a major road face a higher risk of RA by 31% compared with those living more than 200 meters away (10). However, there was no risk associated with specific air pollutants, including PM2.5, NO, and SO2, in the same population (11).

Although the pathogenic mechanisms of RA are still unknown, prior research has presented that air pollution exposure causes an increase in the levels of interleukin-6 levels and tumor necrosis factors; hence, it may stimulate tissue-specific inflammation (2).

The World Health Organization (WHO) reported air pollution as the 13th leading risk factor for death worldwide, causing 800,000 deaths annually (12). However, there is still a lack of sound evidence to demonstrate the association between the risk of RA and air pollution from previous well-designed epidemiological studies (2). Further studies are required to evaluate the severe and potential effects of air pollutants on rheumatic diseases and the mechanisms of the onset and exacerbation of such diseases (13). In summary, available evidence presented a remarkable link between air pollutants (ozone, residential proximity to traffic road PM2.5) and RA. Nevertheless, further studies should be conducted in developing countries with a higher level of air pollution to provide a comprehensive understanding of risk factors for RA (14). Therefore, this study aimed to determine the effect of air pollutants on disease activity and quality of life in RA patients by a longitudinal design, considering different confounders, notably medications, seasons, and jobs. Another advantage of this study is that it calculates air pollutants at major weather stations in the patients' neighborhoods rather than only focusing on the overall level of air pollution in a densely populated area.

Methods

This longitudinal prospective observational study was conducted in a metropolis in Iran with a high level of air pollution. The study population included RA patients referred to the Rheumatic Diseases Research Center (RDRC) in Mashhad between winter 2017 and autumn 2018. Patients were enrolled in the study consecutively after giving informed consent based on the inclusion criteria. For each patient, the assessment course was 6 months with bimonthly intervals of visits during the winter and spring, which were performed from the time of entrance into the study, and the first course of metrological data was gathered the months before the first physical examination.

Inclusion Criteria

All enrolled patients were Mashhad citizens diagnosed with RA according to the 2010 ACR/EULAR classification criteria for RA (15).

Exclusion Criteria

We considered the following criteria to exclude patients during the onset phase or within the research process:

1. Long suburban travel out of Mashhad throughout the study,
2. Facing severe stress (first-degree relative death, divorce, legal or economic problems, as the patient complains), which can lead to flare,
3. Arbitrary discontinuation of medication,
4. Passive or active smokers,
5. Suffering from cardiovascular, respiratory, liver disease, new-onset diabetes, pregnancy, and hospitalization for any other illness, and
6. Daily commuting to another central meteorological station.

Data Collection

Patient interviews and physical examinations were performed in urban field data gathering.

The data collection tools were as follows (16-19):

- The demographic information checklist,
- Disease Activity Score-28ESR (DAS28ESR),
- the Health Assessment Questionnaire (HAQ),
- Physical health Component Summary (PCS),
- Visual Analogue Scale (VAS), and
- Meteorological checklist.

The meteorological checklist for our analysis included monthly and seasonal information about temperature, relative humidity, and percentage of polluted days, NO, CO, SO_2, PM10, and PM2.5 for every 2 months' follow-up intervals that were recorded from the earliest meteorological station of patents' domicile. The mean for each item mentioned above over 2 months before each visit entered the statistical analysis. Moreover, the checklist of demographic information included gender (male/female), age (year), job position, marital status (single/married), place of residence (name of the nearest meteorological station), duration of illness (year), and their current medications (name of drug and dosage), which was completed over the interviews.

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The assessment courses were performed at bimonthly intervals from the time of entrance into the study for each patient. The data on the DAS28ESR and medications and other responses to variables such as the HRQoL by the HAQ and PCS and VAS were collected in these periodic visits. For the first visit, all patient with a DAS28ESR score of more than 3.2 were selected as active disease patients, Table 1 presents the mean DAS score of patients on the first visit as 3.74 ± 1.49.

Sample Size

In our study, regarding the regression test analysis variables, we considered the DAS28ESR score as a dependent variable, whereas PM10, NO, CO, and PM2.5 were determined as independent variables, similar to the study of Bernatskys et al (20). We considered 10 samples for each independent variable, and concerning the alpha and beta values ($\alpha = 0.05$; $\beta = 0.2$), the minimum sample size should be 30 patients. Overall, we considered 50 patients.

Execution Steps

We registered the checklist, including demographic characteristics, duration of disease, and doses of medication per person at the time of inclusion. All information about the patients and meteorological data over the 2 months before the first physical examination was applied to the data collection sheet. Afterward, scales, including the DAS28ESR, HAQ, PCS, and VAS, were completed. Therefore, patients' data gathering was referred to 2 months before the first visit.

Air pollution information was obtained from the nearest meteorological station to the patient's residential area from the official website of the Mashhad Meteorological Department. Then, the average amount of air pollutants with other variables was calculated and evaluated every 2 months from 2 months before the first visit and then bimonthly until the end of the third visit for each case individually. Given the meteorological data from the pertinent weather station, the percentage of polluted days, temperature, humidity, and the average concentration of air pollutants—such as SO_2, NO, CO, O_2 level, PM2.5, and PM10—were registered in the mentioned period. The number of meteorological stations around Mashhad is 21. Thus, the relationship between disease activity and air pollution over the 3 visits was investigated for 6 months.

Statistical Methods

Frequency and relative frequency were used to describe qualitative variables, while central indices and dispersion—such as mean and standard deviation—were applied to analyze quantitative variables. To demonstrate the variation of variables over the 3 visits, we leveraged the visualization and statistic libraries of the Python programming language[2] (Figure 1).

https://www.python.org/

To assess the effects of meteorological variables on the DAS28ESR, VAS, PCS, and HAQ score, we applied the generalized estimation equation (GEE) method by SPSS-21 software. Important confounding variables, including sex, job (housekeeper, employee, and student), age, medications, and disease duration, were considered in the GEE analysis.

To investigate the relationship between variables, the initial relationship between independent variables and response variables was measured separately (univariate); then, according to their importance, all independent variables were entered simultaneously (multivariate). Eventually, they were modeled to measure the relationship between independent variables and other variables and response variables. The significance level was considered at

Table 1. Statistical difference between Mean ± SD of meteorological, disease activity and medications in 3 visits of patients with rheumatoid arthritis

Variable Time	Visit 1	Visit 2	Visit 3	*P* Value*	*P* Value**	*P* Value***
Meteorological Data						
Humidity (%)	63.95±14.59	50.77±9.87	29.21±8.65	P<0.001	P<0.001	P<0.001
Temperature (0C)	5.58±3.76	17.39±6.06	25.72±2.48	P<0.001	P<0.001	P<0.001
Air pollutants						
Polluted days (%)	40.62±18.91	26.98±14.53	24.58±21.42	P<0.001	0.130	P<0.001
CO concentration (ppm)	1.99±1.07	1.61±0.93	0.26±0.49	0.042	0.015	P<0.001
O2 level (ppb)	47.62±31.71	42.26±27.66	43.44±26.79	0.237	0.751	0.346
PM2.5 ($\mu g/m^3$)	35.54±8.61	32.54±9.80	28.90±10.90	0.130	0.027	0.003
NO (ppb)	41.68±29.97	47.76±29.32	40.12±28.00	0.274	0.797	0.205
SO_2(ppb)	11.61±2.75	8.99±3.67	8.14±3.63	P<0.001	0.042	P<0.001
PM10($\mu g/m^3$)	49.75±19.85	56.27±19.39	49.79±15.32	0.099	0.001	0.989
Medications						
Prednisolone	4.35 ± 2.13	4.2±2.11	3.85±2.86	0.705	1.000	0.778
Methotrexate	11.05±4.95	12.2±4.61	9.8±4.43	0.370	0.974	0.438
Inflammatory Indices and Response variables						
ESR	23.46±17.47	22.50±14.47	21.72±15.89	0.771	0.634	0.502
DAS28ESR (Disease Activity Score 28ESR)	3.74±1.49	3.56±1.34	3.36±1.42	0.403	0.364	0.110
HAQ (Health Assessment Questionnaire)	0.57±0.81	0.48±0.47	0.41±0.40	0.253	0.379	0.185
PCS (physical health component summary)	0.97±0.69	1.05±0.78	1.00±0.75	0.253	0.657	0.819
VAS (Visual Analogue Scale)	32.2± 26.9	29.2±25.2	28.50±24.41	0.425	0.857	0.363

* *P* value of parameters' difference between visit 1 and visit 2
** *P* value of parameters' difference between visit 2 and visit 3
*** *P* value of parameters' difference between visit 1 and visit 3 (Onset and Final)

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$\alpha = 0.05$ ($P < 0.05$).

Ethical Considerations

After being informed of the study's purpose and methodology, participants were required to sign informed consent forms. The Medical Ethics Committee approved the present study (Code: IR.MUMS.fm.REC.1395.355).

Results

After the first screening by researchers, 78 RA patients consecutively were referred to our research center throughout the study. However, 28 patients were excluded from the study based on the exclusion criteria in the secondary screening.

Overall, there were 50 participants, including 46 women (92%) and 4 men (8%). The mean age of the participants was 54.24 ± 12.17 years. The mean disease duration was 7.76 ± 7.6 years. Also, 43 (86%) of the participants were housewives and 7 (14%) were employees. The mean of medications' doses, response variables (HAQ, DAS28ESR, PCS, VAS), and meteorological variables during the study are represented in Table 1.

Table 1 also presents the analysis of central and dispersion indices (such as mean and standard deviations) for quantitative variables such as air pollutants, percent of polluted days, humidity, temperature, disease activity indices (DAS28ESR, HAQ, PCS, and VAS), the dose of prednisolone and methotrexate in each visit, and the P value between every 2 visits. Despite significant changes in metrological parameters and some air pollutant variables (ie,

Table 2. Statistical analysis by the GEE Method on patients clinical, meteorological parameters, air pollutants, temperature and humidity according to disease activity score (DAS) and health assessment questionnaire (HAQ)

Disease Disability and Activity Measurers		HAQ (GEE Method)				DAS28ESR (GEE Method)			
Variables	Groups	Univariate analysis B (se)	*P*-value	Multivariate analysis B (se)	*P*-value	Univariate analysis B (se)	*P*-value	Multivariate analysis B (se)	*P*-value
Qualitative variables									
Sex	Men	-0.17 (0.24)	0.468	0.27 (0.19)	0.172	0.005 (1.03)	0.992	0.35 (0.75)	0.638
	Women	---	---	---	---	---	---		
Job	Employee	-0.06 (0.097)	0.489	-0.023 (0.16)	0.878	-0.97 (0.42)	0.023	-0.84 (0.45)	0.059
	Self employed	-0.49 (0.08)	<0.001	-0.39 (0.15)	0.013	-1.21 (0.41)	0.003	-0.89 (0.30)	0.003
	Housekeepers	---	---	---	---	---	---	----	---
Season	Spring	-0.07 (0.08)	0.374	0.07 (0.16)	0.673	-0.11 (0.18)	0.538	0.17 (0.37)	0.657
	Summer	-0.19 (0.11)	0.098	0.14 (0.19)	0.472	-0.39 (0.23)	0.092	-0.09 (0.49)	0.847
	Winter	---	---	---	---	---	---	---	---
Quantitative variables									
Age	---	0.001 (0.005)	0.801	-0.003 (0.005)	0.557	-0.006 (0.01)	0.648	-0.01 (0.014)	0.394
Disease Duration	---	0.02 (0.012)	0.112	0.008 (0.01)	0.512	0.03 (0.026)	0.181	0.002 (0.02)	0.931
Medications (qualitative)									
Rituximab ($2gr/6$ month)	Yes	0.22 (0.12)	0.067	0.02 (0.13)	0.881	0.36 (0.36)	0.324	-0.16 (0.25)	0.498
	No	---	---	---	---	---	---	---	---
Infliximab (3mg/kg/ 2 month)	Yes	0.22 (0.12)	0.064	0.02 (0.13)	0.878	-1.07 (0.07)	0.001	-0.33 (0.34)	0.327
	No	---	---	---	---	---	---	---	---
Adalimumab (40mg/ 2 weekly)	Yes	0.33 (0.21)	0.111	0.15 (0.25)	0.539	0.39 (0.68)	0.574	0.04 (0.43)	0.928
	No	---	---	---	---	---	---	---	---
Etanercept(50mg/weekly)	Yes	0.15 (0.16)	0.348	-0.07 (0.19)	0.715	0.39 (0.26)	0.132	0.56 (0.25)	0.022
	No	---	---	---	---	---	---	---	---
Joint Injections	Yes	0.32 (0.16)	0.052	-0.25 (0.26)	0.338	1.43 (0.49)	0.004	0.03 (0.35)	0.943
	No	---	---	---	---	---	---	---	---
Medications (quantitative)									
Prednisolone (mg/d)	--	0.07 (0.02)	0.008	0.06 (0.02)	0.005	0.19 (0.05)	0.001	0.17 (0.04)	0.001
Methotrexate (mg/week)	--	0.03 (0.023)	0.164	0.02 (0.018)	0.214	0.051 (0.032)	0.126	0.015 (0.03)	0.587
Meteorological data									
Humidity (%)	--	0.003 (0.002)	0.141	-0.002 (0.004)	0.596	0.006 (0.005)	0.221	-0.008 (0.007)	0.272
Temperature (0^C)	--	-0.007 (0.004)	0.094	-0.01 (0.013)	0.214	-0.014 (0.01)	0.185	-0.02 (0.02)	0.448
O_2 level (%)	--	-0.001 (0.001)	0.412	-0.001 (0.001)	0.276	-0.002 (0.005)	0.718	-0.003 (0.004)	0.439
Air pollutants									
Polluted days (%)	--	-0.02 (0.16)	0.867	-0.11 (0.18)	0.563	0.004 (0.005)	0.417	0.01 (0.006)	0.094
CO Concentration (ppm)	--	0.08 (0.08)	0.283	0.03(0.06)	0.617	0.19 (0.1)	0.063	0.04 (0.08)	0.013
$PM_{2.5}$ ($\mu g/m^3$)	--	-0.001 (0.001)	0.458	0.005(0.005)	0.245	-0.008 (0.009)	0.361	-0.02 (0.012)	0.086
NO_2 (ppb)	--	-0.001 (0.001)	0.458	-0.001 (0.001)	0.232	-0.001 (0.006)	0.868	-0.003 (0.003)	0.286
SO_2 (ppb)	--	-0.001 (0.001)	0.458	-0.01(0.01)	0.224	0.039 (0.028)	0.172	-0.003 (0.03)	0.918
PM_{10} ($\mu g/m^3$)	--	0.002 (0.002)	0.291	-0.04 (0.13)	0.771	-0.001 (0.006)	0.868	-0.004 (0.003)	0.334

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Table 3. Statistical analysis by the GEE method on patients clinical, meteorological parameters, air pollutants, temperature and humidity according to visual analogous scale (VAS) and physical health component summery (PCS)

Disease Activity Measurers		VAS (GEE Method)				PCS (GEE Method)			
Variables	Groups	Univariate analysis B(se)	*P*-value	Multivariate analysis B(se)	*P*-value	Univariate analysis B(se)	*P*-value	Multivariate analysis B(se)	*P*-value
Qualitative variables									
Sex	Men	6.38 (14.05)	0.647	9.40 (14.21)	0.512	0.13 (0.43)	0.758	0.18 (0.41)	0.648
	Women	---	---			---	---	---	---
Job	Employee	-18.2 (6.83)	0.008	-19.43 (9.23)	0.033	0.02 (0.29)	0.949	-0.27 (0.34)	0.432
	Self employed	-12.93(8.17)	0.114	-18.22 (6.84)	0.008	-0.61 (0.21)	0.003	-0.7 (0.19)	0.001
	Housekeepers	---	---			---	---		
Season	Spring	-1.44 (3.52)	0.682	14.4 (9.4)	0.124	0.14 (0.1)	0.174	0.38 (0.27)	0.163
	Summer	-2.01 (4.29)	0.639	16.45 (12.82)	0.187	0.06 (0.12)	0.599	0.3 (0.42)	0.469
	Winter	---	---	---	---	---	---	---	---
Quantitative variables									
Age	---	0.11 (0.25)	0.657	0.16 (0.28)	0.569	-0.004 (0.007)	0.568	-0.003 (0.008)	0.688
Disease Duration	---	0.32 (0.49)	0.514	-0.26 (0.5)	0.612	0.02 (0.01)	0.253	-0.002 (0.015)	0.887
Medications (qualitative)									
Rituximab ($2gr/6$ month)	Yes	5.23 (6.54)	0.424	5.78 (5.23)	0.267	0.34 (0.18)	0.052	0.39 (0.21)	0.064
	NO	---	---	---	---	---	---	---	---
Infliximab ($3mg/kg/2$ month)	Yes	-17.8 (1.6)	0.001	-25.29 (7.22)	0.001	-0.66 (0.04)	0.001	-1.31 (0.21)	0.001
	No	---	---	---	---	---	---	---	---
Adalimumab (40mg/ 2 weekly)	Yes	4.43 (12.23)	0.723	-7.08 (12.12)	0.563	0.57 (0.17)	0.001	-0.56 (0.28)	0.042
	No	---	---	---	---	---	---	---	---
Etanercept(50mg/weekly)	Yes	5.24 (4.18)	0.211	2.43 (5.19)	0.637	0.06 (0.23)	0.788	0.09 (0.18)	0.586
	No	---	---	---	---	---	---	---	---
Joint Injections	Yes	27.61 (4.52)	0.001	7.66 (7.22)	0.291	0.54 (0.41)	0.183	0.05(0.23)	0.824
	No	---	---	---	---	---	---	---	---
Medications (quantitative)									
Prednisolone (mg/d)	--	2.73 (0.91)	0.003	2.44 (1.01)	0.012	0.08 (0.02)	0.001	0.08 (0.02)	0.001
Methotrexate (mg/week)	--	0.7 (0.43)	0.124	0.39 (0.49)	0.424	0.02 (0.01)	0.052	0.009 (0.013)	0.458
Meteorological data									
Humidity (%)	--	0.02 (0.09)	0.788	-0.16 (0.13)	0.228	-0.002 (0.003)	0.396	-0.007 (0.01)	0.467
Temperature (0^C)	--	-0.12 (0.18)	0.514	-0.71 (0.61)	0.239	0.004 (0.005)	0.396	-0.01 (0.024)	0.978
O_2 level (%)	--	-0.06 (7.7)	0.988	-0.19 (8.95)	0.981	-0.005 (0.23)	0.982	0.06 (0.21)	0.772
Air pollutants									
Polluted days (%)	--	13.68 (10.39)	0.182	28.5 (11.38)	0.013	-0.12 (0.25)	0.623	0.31 (0.23)	0.184
CO Concentration (ppm)	--	4.48 (1.73)	0.012	3.88 (1.83)	0.034	0.09 (0.04)	0.053	0.09 (0.05)	0.084
$PM_{2.5}$ ($\mu g/m^3$)	--	-0.12 (0.17)	0.459	-0.26 (0.2)	0.192	-0.005 (0.004)	0.248	-0.004 (0.005)	0.988
NO_2 (ppb)	--	-0.09 (0.08)	0.263	-0.07 (0.07)	0.268	-0.002 (0.002)	0.267	-0.002 (0.002)	0.178
SO_2 (ppb)	--	0.62 (0.57)	0.274	0.16 (0.69)	0.818	-0.003 (0.01)	0.858	0.004 (0.017)	0.812
PM_{10} ($\mu g/m^3$)	--	-9.9 (8.52)	0.241	-6.73 (9.47)	0.467	-0.04 (0.3)	0.879	-0.04 (0.3)	0.886

number of polluted days and CO), it is indicated that disease activity, quality of life indices, and medications as a surrogate of disease activity have not changed significantly during the study.

The first visit of 4 (8%) and 46 (92%) patients began in the spring and winter, respectively. In the second round, 37 patients (74%) in the spring, 3 (6%) in the summer, and 10 (20%) in the winter were visited. For the last visit in the spring and summer, the number of patients was 11(22%) and 39 (78%), respectively. The relationships between standard measuring tools (DAS28ESR, HAQ, PCS, and VAS) for disease activity and quality of life and different confounders and meteorological variables using the Gee analysis test are presented in Tables 2 and 3.

The types and doses of medications used by patients during the visits are varied based on the changes in disease activity, which is unavoidable due to ethical issues. The medication types and doses are summarized in Table 1. and the medication types were also applied in the GEE analysis for each disease activity indicator separately (Tables 2 and 3). Methotrexate and prednisolone doses, which are critical for leaving out drug bias, did not vary considerably during the study in our patients. Statistical analysis of patients' data indicated a significant influence of CO concentration on the increase of disease activity (DAS28ESR) (Table 2). Furthermore, the increasing effect on the VAS with higher CO concentration and the percentage of polluted days was shown at the level of $\alpha = 0.05$, demonstrating that greater CO concentrations and polluted days were associated with patients reporting their illness condition (Table 3).

We leveraged the linear regression algorithm with marginal distribution to measure the effect of CO concentration and disease activity, and we found a significant relationship between these 2 variables. The effect of CO pollutants on the DAS28ESR and VAS, in general, is shown in Figure 1. The response variables (VAS, DAS28ESR, PCS, and HAQ) did, however, vary across all visits.

Discussion

Several studies revealed that the morbidity and mortality

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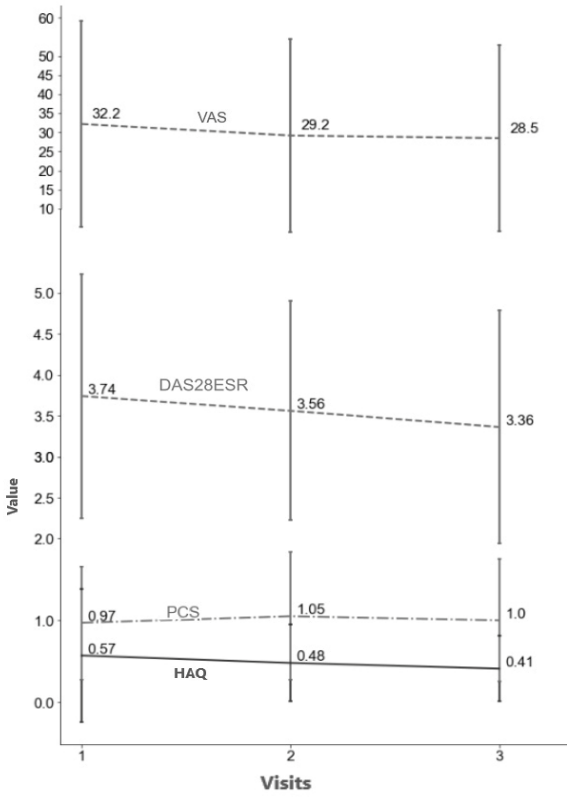

Figure 1. Variations in visual analogous scale (VAS), disease activity score (DAS28ESR), quality of life (HAQ), and PCS (Physical health Component Summary) (X-axis shows the 3 visits and Y-axis shows the range of each variable during our study).

rates, predominantly in respiratory and cardiovascular systems were conventionally influenced by air pollutants. This study aimed to determine the effect of air pollutants on disease activity and quality of life in RA patients in Mashhad in 2018. Our data analysis indicated a significant negative influence of CO concentration on the VAS and DAS28ESR. Moreover, a number of polluted days increased VAS scores in patients.

A cross-sectional study in Italy in 2021 investigated the effect of short-term (7 days before enrolment) exposure to particulate matter PM10, PM2.5, NO_2, and O_3 on RA disease activity (DAS28 and SDAI). Therefore, some positive associations emerged between O_3 and disease activity (21).

In 2001, Leonardi et al conducted a survey in 17 cities with a wide range of outdoor air pollution representation in a short period of 1 month. They measured the association between serum immune biomarkers (such as lymphocytes and total immunoglobulin) of 366 school children and the air ambient PM2.5 and PM10. The results indicated differences in lymphocyte number, higher total IgG, and statistically significant exposure to PM2.5. Although our investigation involved long-term exposure to airborne particles, these 2 studies were completed in a limited amount of time (6 months). Therefore, this issue could be one possible interpretation of our different findings (22).

In 2016, Chiang et al studied the association between urbanization and RA. Their findings were in line with other major epidemiological studies and confirmed this correlation; meanwhile, they noted that RA incidence was higher in urban areas than in rural areas (23).

A longitudinal and nationwide study in Taiwan observed that NO levels but not PM2.5 are related to increased risk of RA (2). However, Roos et al did not detect associations between RA and air pollution (PM2.5 and NO). The mentioned results indicated increased RA risk in participants with residence ≤50 m from a highway (8). These findings confirmed the NHS study in Canada and acknowledged that exacerbation of disease activity had increased by 31% in short-distance residency (≤50 m) compared with long distances (more than 200 meters) from roadways (10). The issue of how far patients live from polluted places is not considered in detail in our study. In contrast, the average air pollution in each area was measured with the relevant meteorological station. Hence, this difference might lead to changes in our conclusion.

In 2020, autoantibody status and exposure to ambient air pollution in RA were evaluated in a cohort study. In univariate and multivariable regression models, PM2.5 exposures were associated with higher anti-citrullinated protein antibody concentration ($P = 0.009$ and $P = 0.037$, respectively) (24). Therefore, this study suggests an association between air pollution and RA-related antibodies, in line with our study.

Alsaber et al investigated the influence of ambient air pollution on the DAS28ESR in 2020. They detected a strong association between SO_2 and NO concentration and an increased risk of RA (25). Another cohort study of patients followed over 5 years, revealed an essential link between air pollution and RA disease severity and reactivations. Exposure to greater air pollutants, including CO, NO, PM10, PM2.5, and O_3, brings about a higher risk of having CRP levels ≥5 mg/L (26). These 2 studies were compatible with our findings on the negative effect of CO concentration on RA activity. In our study, the ESR increased as an inflammatory marker, while the CRP showed a similar response (26).

In a 5-year study in 2021, Adami et al observed that a 60-day exposure to ambient air pollution was the determining factor in the poor response to biologic disease-modifying antirheumatic drugs (DMARDs) in a group of chronic inflammatory arthritis (CIA), particularly RA patients. To better predict the effectiveness of CIA treatments, it is critical to understand how air pollution affects the response rate to biologic DMARDs (27).

Determining a safe level of particulate matter and air pollutants is necessary to predict at least partially their adverse effects on systemic inflammation, autoimmunity, and other disease development. There is still no worldwide consensus on permissible levels of air pollutants. Therefore, the WHO Air quality guideline values were chosen as our study criteria—including fine particulate matter (PM2.5): 10 μg/m^3 annual mean and 25 μg/m^3 24-hour mean; coarse particulate matter (PM10): 20 μg/m^3 annual mean and 50 μg/m^3 24-hour mean; and NO: 40 μg/m^3 annual and 200 μg/m^3 24-

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hour mean. However, those values are not a definite threshold for autoimmunity if this relation exists. In our study, the mean values of PM2.5, PM10, and NO (over 2 months and around 6 months) were more than the safe cutoff points aforementioned (28). A time-series approach (Wu et al, 2021) investigated the short-term association between traffic-related air pollutants (PM2.5, PM10, NO, CO) and daily hospital readmissions for RA in China. The results asserted that the high concentration of PM2.5 and NO in cold seasons were significantly related to the increased risk of RA readmissions (29).

Our study found no correlation between seasons and disease activity by considering air pollutants. The co-occurrence of cardiovascular and respiratory diseases in the cold seasons of the year might have affected the readmission of patients, which should be explained as confounding factors. The Wu et al study was not mentioned in the method.

In 2020, Han performed a cross-sectional survey using the East Asian Social Survey 2010 data on Chinese populations regarding environmental pollution. The HRQoL was computed by the 12-item short-form survey and reflected by the PCS & MCS scores.

It indicated that perceived air pollution had significant associations with PCS and MCS scores (16).

Various studies have demonstrated the association between RA and specific pollutants in low- and middle-income communities. The results suggested a correlation between tropospheric pollutants and RA. It could play a confounder role that could explain the lack of correlation between air pollution and disease activity in the NHS study in the United States (1, 10).

Our study's longitudinal design, consideration of numerous confounders, medication and dose adjustments, seasons, and jobs were some of its numerous advantages. Computing air pollutants in main meteorological stations close to the patient's residence instead of the global air pollution, excluding other reasons for disease exacerbations such as major emotional stressors and other comorbidity flares, passive and active smoking exposure, and long suburban travels out of the study site could be defined as the other strengths of the study. Even though our study took into account 3 different professional statuses (employee, housewife, and others), the majority of patients were female housekeepers who had modified outdoor activities near meteorological stations. Hence, the extent of outdoor exposure is necessary; and determining the average amount of time exposed to air pollution in different occupations in more detail might be beneficial in future studies. The results present a significant relationship between disease activity and VAS with CO concentration. According to most similar studies on the Chinese population, there might be substantial differences in epidemiological, demographic, and ecological features with our study population that need to be investigated by widespread comprehensive studies in the future.

Conclusion

In this study, we investigated the effect of air pollutants on RA disease activity and quality of life. Based on our findings, air pollution, particularly CO concentration, has affected at least disease activity and pain score (VAS) in RA patients. To generalize and confirm these findings, further research is needed.

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Data Availability Statement

The authors confirm that the data supporting the findings of this study are available in the article and its supplementary materials.

Conflict of Interests

The authors declare that they have no competing interests.

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