

CONCISE REPORT

Relationship between air pollution and positivity of RA-related autoantibodies in individuals without established RA: a report on SERA

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ABSTRACT

Introduction Studies suggest that respiratory exposures including smoking, proximity to traffic and air pollution might be associated with development of rheumatoid arthritis (RA). RA-related autoantibodies are predictive of the development of RA.

Objective We evaluated the relationship between RA-related autoantibodies and exposure to particulate matter (PM), a measure of air pollution of interest to health, in individuals without RA.

Methods The Studies of the Etiology of Rheumatoid Arthritis (SERA) is a multicentre study following first-degree relatives (FDRs) of a proband with RA. FDRs are without the 1987 ACR (American College of Rheumatology) classifiable RA at enrolment and are followed for the development of RA-related autoimmunity. RA-related autoantibody outcomes as well as tender and swollen joint outcomes were assessed.

Exposure to PM was assigned using ambient air pollution monitoring data and interpolated with inverse distance weighting spatial analyses using Geographic Information Systems. PM exposures were linked to FDR's residential zip codes.

Results RA-related autoantibodies as well as tender or swollen joints are not associated with ambient PM concentrations.

Discussion While other respiratory exposures may be associated with increased risk of RA, our data suggest that ambient PM is not associated with autoantibodies and joint signs among individuals without RA, but at increased risk of developing RA.

INTRODUCTION

Seropositive rheumatoid arthritis (RA) is characterised by abnormal elevations of circulating rheumatoid factor (RF) autoantibodies and inflammatory arthritis, which can cause lifelong disability and reduced lifespan.¹ These autoantibodies are present in the blood years before clinical diagnosis of RA, suggesting that the factors initiating RA-related autoimmunity are acting prior to the appearance of joint symptoms and other signs characteristic of clinically apparent disease.^{2–4} The aetiology of RA remains unknown; however, study of the early period of RA development to identify environmental risk factors associated with RA-related autoantibodies could prove useful in elucidating RA pathogenesis.

Exposures to cigarette smoke and silica dust are associated with increased risk of RA, suggesting that

airborne exposures might elicit an autoimmune response.^{5–7} Furthermore, we recently reported an increased proportion of inflammatory airway abnormalities in autoantibody-positive subjects and early RA cases compared with autoantibody-free controls—differences that persisted even in non-smoking subjects, suggesting that initial inflammation in RA and generation of RA-related autoantibodies may begin in the lungs, and perhaps be related to inhaled factors besides tobacco smoke.⁸ Such a factor might be air pollution, an inhaled exposure that has been linked to numerous poor health outcomes, with evidence suggesting an effect on autoimmune diseases as well.^{9–10} Furthermore, the Nurses' Health Study reported an elevated risk for RA in women living in close proximity to major roadways, which may be a surrogate for air pollution.¹¹

The Environmental Protection Agency (EPA) collects data throughout the USA on six common measures of ambient air pollution, one of which is particulate matter (PM), composed of microscopic particles and liquid droplets, with concentrations measured in microgram per cubic metre for two particle sizes: particles 10 µm or smaller in diameter (PM₁₀) and 2.5 µm or smaller in diameter (PM_{2.5}). Both variants of PM can enter the respiratory tract, with PM_{2.5} capable of entering the alveoli. Environmental variability of air pollution and difficulty in collecting personal exposure make indirect measurements ideal for assessing exposure. Geographic Information Systems (GIS) offers a novel way to evaluate aggregate measures of air pollution exposure, previously used to model air pollution to evaluate health outcomes including, but not limited to, asthma and increased mortality.^{12–13} Recently, researchers have evaluated air pollution, that is, PM₁₀, nitrogen dioxide (NO₂) and sulphur dioxide (SO₂) levels mapped to resident addresses, and found no consistent differences in exposure between RA cases and controls.¹⁴ No studies have examined air pollution using the presence of RA-related autoantibodies as an outcome.

To explore the hypothesis that inhaled exposures may act early in the pathogenesis of RA and lead to the generation of RA-related autoimmunity, we evaluated the association between exposure to air pollution, measured by average annual PM_{2.5} and PM₁₀, and the presence of RA-related autoantibodies as well as the joint outcomes that may be indicative of early inflammatory arthritis.

METHODS

The study population was derived from the Studies of the Etiology of Rheumatoid Arthritis (SERA), a multicentre, prospective cohort study of first-degree relatives (FDRs) of probands with RA. Participants were enrolled in Denver, Los Angeles, Chicago, New York, Nebraska and Seattle. Enrolment began in 2002 and continued until 2012, with 1767 participants and 3280 visits at the time of this study. FDRs received an initial examination confirming that they did not have RA meeting the 1987 American College of Rheumatology (ACR) criteria,¹⁵ and subsequent follow-up visits to collect blood for measurement of the following autoantibodies: anticyclic citrullinated peptide (anti-CCP2), RF by nephelometry and RF isotypes such as immunoglobulin (Ig) A, G and M (RF-IgA, RF-IgG, RF-IgM), described previously.¹⁶ We evaluated the following outcomes: RF positivity, high-risk autoantibody profile (HRP) positivity, which was defined as positivity for anti-CCP2 and/or two RF isotypes, and a measurement of inflammation, high-sensitivity C-reactive protein (hsCRP) positivity, as described previously.¹⁶ We were unable to investigate anti-CCP2 alone as we had only 28 anti-CCP2 positives; however, HRP was found to be 74% sensitive and 98.6% specific for RA, which was comparable to anti-CCP2.⁴ In addition, tender or swollen joint outcomes (≥ 1 affected joint) were assessed by a 68-count joint examination administered by a trained study physician or nurse. Tender or swollen joints, due to degenerative joint disease or injury, or of the first metatarsophalangeal joint (commonly associated with osteoarthritis) were not included in this outcome.

Yearly averages for PM_{2.5} and PM₁₀ were assessed using data from the EPA's air monitoring system for California, Colorado, New York, Washington and Nebraska as these states had the largest number of FDRs. Zip code of residence for each visit was used to assign averaged PM exposure for the year of that SERA visit. From 2002 through 2011, PM_{2.5} and PM₁₀ data from each state's monitoring stations were averaged annually and then geocoded into ArcGIS V. 10. Inverse distance weighted (IDW) spatial analyses, a method used to evaluate ambient air pollution exposure with other health outcomes,¹⁷ interpolated the averaged PM exposures for each year. PM₁₀ was not interpolated for New York as there were no available EPA data. The IDW method uses the specific yearly averages from air monitoring stations within a region, the state in this case, to interpolate yearly averages to areas not in close proximity to an air monitoring station. Yearly average values of PM_{2.5} and PM₁₀ from stations closer in proximity provide more weight to interpolated values than stations farther away. Because of this, only FDRs with a resident zip code centroid located within 50 km of an air monitoring station were included, to reduce the potential for exposure misclassification. PM exposures derived from these interpolations were linked with FDRs based on their resident zip codes. There were 979 FDRs with a total of 1730 visits assigned a PM_{2.5} exposure and 836 FDRs with a total of 1371 visits assigned a PM₁₀ exposure.

Associations between the dichotomous autoantibody, hsCRP, and joint outcomes and continuous PM were tested using non-linear (logistic) mixed models, which account for multiple visits per subject. Results are reported as ORs, indicating the difference in the risk for the outcome for an increase in SD in PM.

RESULTS

Our study population lived in Colorado (39%), California (29%), Nebraska (13%), Washington (11%) and New York (8%) (see online supplementary map figure S1). Table 1 presents

Table 1 Description of FDR population at initial visit comparing those positive for each outcome (pos.), to those negative for each outcome (neg.)

Demographics	HRP†			RF			hsCRP			Tender joint			Swollen joint		
	Pos. n=44	Neg. n=796	p	Pos. n=47	Neg. n=793	p	Pos. n=231	Neg. n=609	p	Pos. n=56	Neg. n=769	p	Pos. n=92	Neg. n=733	p
Age, mean±SD	43.4±15.9	45.3±15.7	0.43	51.1±16.3	44.8±15.6	<0.01	47.7±15.7	44.2±5.6	<0.01	49.4±16.1	44.9±15.8	0.04	48.7±16.0	44.8±15.6	0.03
PM _{2.5} (µg/m ³) mean±SD	10.5±3.2	10.3±2.8	0.58	10.0±2.9	10.3±2.8	0.49	10.2±2.7	10.4±2.9	0.37	9.7±2.7	10.4±2.6	0.10	10.2±2.9	10.4±2.9	0.58
PM ₁₀ (µg/m ³) mean±SD‡	27.2±6.5	26.8±5.7	0.63	26.1±6.8	26.9±5.6	0.41	26.8±5.6	26.8±5.8	0.89	26.6±5.0	26.8±5.8	0.75	27.0±5.7	26.8±5.7	0.70
Gender: female (%)	75.0	69.6	0.45	70.2	69.9	0.96	77.1	67.2	<0.01	80.4	68.8	0.07	76.1	68.8	0.15
Race, NHW (%)	75.0	74.3	0.91	74.5	74.3	0.98	72.3	75.0	0.42	73.2	74.5	0.83	78.3	73.9	0.37
Current smoker (%)	15.9	11.6	0.38	12.8	11.7	0.83	11.7	12.1	0.85	8.9	12.0	0.50	10.9	11.9	0.78
>High school (%)	72.7	79.7	0.27	83.0	79.1	0.52	73.6	81.4	0.01	73.2	79.6	0.26	70.7	80.2	0.03
Site (%)															
Denver	29.6	40.2	0.45*	53.2	38.8	0.37*	39.0	39.9	0.23*	60.7	38.8	<0.01*	53.3	38.6	<0.01*
Los Angeles	40.9	28.4		19.2	29.6		27.3	29.7		25.0	29.9		31.5	29.3	
Nebraska	11.4	12.4		10.6	12.5		16.5	10.8		10.7	12.5		9.8	12.7	
Seattle	11.4	10.4		8.5	10.6		8.6	11.2		1.8	9.9		3.3	10.1	
New York	6.7	8.6		8.5	8.5		8.6	8.4		1.8	9.0		2.2	9.3	

*p Value reported is the omnibus test for association of outcome by site.

†HRP is defined as positive for anti-CCP2 and/or two or more RF isotypes.

‡The reduced sample size for PM₁₀ is due to a smaller number of air monitoring stations measuring PM₁₀ at initial visit. For the autoantibody and CRP outcomes, there were 715 FDRs; and for the joint outcomes, there were 713 FDRs.

HRP, high-risk autoantibody profile; hsCRP, high-sensitivity C-reactive protein; NHW, non-Hispanic White; RF, rheumatoid factor.

Clinical and epidemiological research

Table 2 OR and the 95% CIs (95% CI) for RF, HRP and hsCRP in relation to levels of PM_{2.5} and PM₁₀

	RF positive visits n=110 OR† (95% CI)	HRP* positive visits n=104 OR† (95% CI)	hsCRP positive visits n=450 OR† (95% CI)
PM _{2.5} ‡ n=979 FDRs n=1730 visits	1.36 (0.82 to 2.24)	0.72 (0.43 to 1.20)	0.71 (0.42 to 1.19)
PM ₁₀ ‡§ n=836 FDRs n=1471 visits	1.09 (0.77 to 1.56)	0.76 (0.51 to 1.12)	0.92 (0.61 to 1.38)

*HRP is defined as positive for anti-CCP2 and/or two or more RF isotypes.

†Adjusted for age, ethnicity, gender, current smoking status, education and recruitment site.

‡Continuous variables, the OR represents a change in risk for a 1 SD increase in PM_{2.5} and PM₁₀. The SDs for PM_{2.5} and PM₁₀ were 2.9 µg/m³ and 5.5 µg/m³, respectively.§The reduced sample size for PM₁₀ is due to a smaller number of air monitoring stations measuring PM₁₀. The number of visits positive for the outcome is: 93 for RF, 95 for HRP and 397 for hsCRP.HRP, high-risk autoantibody profile; hsCRP, high-sensitivity C-reactive protein; PM_{2.5}, particulate matter ≤2.5 µm in diameter; PM₁₀, particulate matter ≤10 µm in diameter; RF, rheumatoid factor.

descriptive characteristics and mean PM exposure of FDRs by outcome. Adjusting for age, ethnicity, gender, current smoking status, education and recruitment site, ambient PM_{2.5} and PM₁₀ levels were not associated with autoantibody, hsCRP (table 2) or with joint outcomes (table 3).

DISCUSSION

Our study suggests that exposure to aggregated annual PM is not associated with autoantibody positivity or tender and swollen joints in individuals without the 1987 ACR classifiable RA. We note that there was a non-significant trend towards an inverse association between PM levels and HRP and hsCRP, which is contrary to our *a priori* hypothesis that PM is associated with increased risk of RA-related outcomes. We observed a similar trend as in Hart *et al*¹⁴ where increasing PM₁₀ levels were inversely, but non-significantly associated with RA. It should be noted that Hart *et al* evaluated clinical RA (1987 ACR criteria), while our outcomes were RA-related autoimmunity and joint signs in unaffected individuals, thus providing new information

Table 3 OR and the 95% CIs (95% CI) for tender and swollen joint positivity (≥1 affected joint) in relation to PM_{2.5} and PM₁₀

	Tender joint positive visits n=101 OR* (95% CI)	Swollen joint positive visits n=165 OR* (95% CI)
PM _{2.5} † n FDRs=861 n visits=1509	1.07 (0.71 to 1.63)	1.12 (0.80 to 1.58)
PM ₁₀ †‡ n FDRs=739 n visits=1288	0.95 (0.70 to 1.28)	1.02 (0.79 to 1.32)

*Adjusted for age, ethnicity, gender, current smoking status, education and recruitment site.

†Continuous variables, the OR represents a change in risk for a 1 SD increase in PM_{2.5} and PM₁₀. The SDs for PM_{2.5} and PM₁₀ were 2.8 µg/m³ and 5.1 µg/m³, respectively.‡The reduced sample size for PM₁₀ is due to a smaller number of air-monitoring stations measuring PM₁₀. The number of visits positive for the outcome is 97 for tender joint and 152 for swollen joint.PM_{2.5}, particulate matter ≤2.5 µm in diameter; PM₁₀, particulate matter ≤10 µm in diameter.

that ambient annual PM levels are not associated with early generation of RA-related autoimmunity prior to development of articular RA.

While the possibility of a false-negative result due to insufficient power cannot be ruled out, it is unlikely, as our results for HRP, in particular, were convincingly in the opposite direction of our *a priori* hypothesis. A limitation of the IDW method is the dependency on the density of monitoring stations, although it has been shown to be comparable to more nuanced methods, such as kriging, when monitoring density is sparse,¹⁸ as was the case with all study sites except Los Angeles. The comparable results we obtained when conducting site-specific analyses, and when varying the distance from monitoring station (from 50 km) (data not shown) suggested that sites with a higher density of monitoring stations, and distance, were not driving the overall trends. While it is feasible to evaluate other pollutants, such as SO₂ and NO₂, the limited number of monitoring stations collecting these pollutants would have reduced our sample size by more than 60%. Although the aggregate nature of our exposure variable limits our ability to infer individual-level exposure, interpolation methods using GIS offer a novel and practical alternative to personal sampling when evaluating environmental exposures in relation to autoimmunity.

Our study's approach to evaluate the association between PM and early indicators of preclinical RA, autoimmunity and joint signs, is the first to do so. We were not limited to only evaluating one city or area, as the multicentre SERA cohort allowed us to examine several regions throughout the US, increasing the generalisability of our results as well as the geographical variation of air pollution exposure. While our outcome of RA autoantibodies is an intermediate biomarker for risk of future clinically classifiable RA, additional studies evaluating the association of PM exposure and the risk of developing RA as well as the continued observation of this unique cohort of individuals at risk for RA is important to understanding the role of air pollution in the aetiology of RA.

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Contributors RWG contributed to the concept and design, analysis plan, cleaned and analysed the data, drafted and revised the paper; GOZ contributed to the analysis plan, supervised data analysis and revised the drafted paper; KDD, MKD, MHW, JHB, PKG, TRM, JRO, RMK and VMH contributed to the concept and design and revised the drafted paper; JMN contributed to the concept and design, analysis plan, supervision of data analysis and draft and revision of the paper. All authors approved the submitted version of this paper.

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