Industrial air emissions, and proximity to major industrial emitters, are associated with anti-citrullinated protein antibodies

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ABSTRACT

Objective: To determine the association of anti-citrullinated antibodies (ACPA) with the ambient air pollutants fine particulate matter (PM2.5) and sulfur dioxide (SO2).

Methods: The CARTaGENE first-wave cohort includes 20,000 general population subjects from Quebec (Canada). On a sample of unselected 1586 subjects, we determined serum, ACPA and performed multivariable logistic regression, for the outcome of positive ACPA, assessing for independent effects of our air pollution variables, adjusting for age, sex, smoking, and French Canadian origin. Two models assessed distance to main industrial emitters of PM$_{2.5}$, and of SO2, and two models assessed tons of SO2 and of PM$_{2.5}$ annual emissions. We also assessed associations with PM2.5 regional ambient concentrations estimated with satellite imagery.

Results: Adjusted analyses suggested a positive association between annual industrial PM$_{2.5}$ and SO2 emissions and the presence of ACPA antibodies (OR: 1.02, 95%CI 1.00–1.04 per 10 t of PM2.5 and 100 t of SO2). The data were also consistent with a negative association between the presence of ACPA, and distance to a major industrial emitter of both PM$_{2.5}$ and SO$_2$. We found no association with PM2.5 estimates of ambient levels.

Conclusions: These analyses suggest that exposure to industrial emissions of air pollutants is related to ACPA positivity.

1. . Introduction

Rheumatoid arthritis (RA) is a serious autoimmune rheumatic disease affecting up to 1% of the population. Much remains to be learned about the risk factors for RA. During a pre-clinical course lasting up to several years, RA-related antibodies (particularly anti-citrullinated protein antibodies, ACPA), can be detected even prior to clinical manifestations. Rantapaa-Dahlqvist et al. (2003); Forslind et al. (2004).

Air pollution has also been associated with RA in a few studies, although this has not been consistent (Sun et al., 2016). Issues relating to measurement of air pollution, both in terms of types and timing, may in part explain the inconsistencies in previous reports. We therefore undertook this study to determine the association between industrial emissions of fine particulate matter (PM$_{2.5}$) and sulfur dioxide (SO$_2$)

and the presence of ACPA, in a sample of a large population-based cohort. Most particulate matter is formed from gases emitted from industries and motor vehicles, although some particulate matter is directly emitted from smokestacks and other sources (EPA, 2009). Industrial activities are the largest sources of SO$_2$ emissions followed by fossil fuel combustion from motor vehicles. US EPA (2008).

2. Methods

Our analyses were based within the CARTaGENE cohort, 20,000 general population subjects drawn from four census metropolitan areas: Montreal, Quebec City, Sherbrooke, Saguenay–Lac-Saint-Jean, all in the province of Quebec, Canada. Participants were randomly selected from the provincial health insurance registries (fichier administratif des inscriptions des personnes assure´es de la Re´gie de l'assurance maladie

du Quebec, RAMQ). This excluded residents of First Nations Reserves or long-term health care facilities or prisons. The participants were selected according to the age distribution in these areas to obtain a representative sample. The CARTaGENE sample has an overall concordance in the distribution of socio-demographic characteristics as compared to the general population of Quebec, and the distribution of some common co-morbidity (e.g. hypertension, diabetes) is also comparable.

The baseline cohort data generated on enrolment of subjects (2008–2009) include demographics (age, sex, and self-reported French Canadian ancestry), health data (e.g. self-reported chronic diseases, including RA), smoking habits (current and past), and stored serum (taken at the baseline visit). Our analyses included a random sample of 3600 subjects. Of these, 1586 subjects provided data on residence, including a valid postal code, and these were used for our analyses. Serum ACPA was determined on biobanked sera using the Inova enzyme-linkeimmunosorbent assay (Quanta Lyte, CCP3 IgG: Inova Diagnostics Inc., San Diego, CA).

Within this subsample, we performed multivariable logistic regression models for the outcome of positive ACPA, assessing for independent effect of industrial air pollution exposure (see definitions below), adjusting for age, sex, smoking, and self-reported French Canadian ancestry(since race/ethnicity, age, and smoking have all been suggested as possible determinants of ACAP positivity, we considered them *a priori*). Miriovsky et al. (2010); Diaz et al. (2011); Kumagai et al. (2009). The smoking variable was categorical, capturing current versus past or never smoker status.

Pollution exposures were determined at the level of the postal code, which in Canada is a six-character alphanumeric string associated with one or more mail delivery points. One postal code serves on average about 20 households.

Exposure to industrial air pollutant emissions were determined from residential proximity (based on baseline six digit postal code of residence) to industrial $PM_{2.5}$ or SO2 emitters, estimated using the National Pollutant Release Inventory (NPRI). The NPRI is Canada's legislated, publicly-accessible database of pollutant releases, disposals and transfers by facilities. Over 8700 facilities report to the NPRI, providing comprehensive air pollutant emission data for contaminants affecting air quality, including $PM_{2.5}$ and SO_2.

Our analyses of the effects of pollution on ACPA antibodies were assessed with five logistic regression models as follows; using the baseline residential postal code for each subject, two separate models assessed distance to main industrial emitters of $PM_{2.5}$ and of SO_2, and two models assessed tons of $PM_{2.5}$ and SO_2 annual industrial emissions, while the remaining model assessed regional satellite $PM_{2.5}$. As has been done in the past (Brand et al., 2016) 'main' emitters were defined as any industry emitting more than an average of 100 t of either $PM_{2.5}$ or SO_2 for at least 5 continuous years from 2002 to 2010; all individuals at a distance larger than 7.5 km (km) from a main emitter were given the distance value of 7.5 km. Industrial emissions of $PM_{2.5}$ and SO_2 in 2008 were summed up for all industries (main emitters or not) within 2.5 km of each postal code.

We also used regional PM2.5 levels estimated from satellite imagery, produced with the Moderate Resolution Imaging Spectroradiometer and multi-angle imaging spectroradiometer systems. Information from these images has been interpreted using the chemical transport model of atmospheric compositions (Goddard Earth Observing System, GEOS-Chem) to estimate regional PM2.5 levels with a geographic resolution of 10×10 km units. Estimates of long-term PM2.5 averages (2001–2006) have been developed based on aerosol optical-depth data from satellite instruments. van Donkelaar et al. (2010) All six digit postal codes located within a 10×10 km cell were given the same regional PM2.5 levels.

Sensitivity analyses were done to decompose the exposure variables as suggested by Leffondre et al., 2002 (Leffondre et al., 2002) into two exposure variables, one binary (coded 1 for exposed and 0 for

Table 1
: Baseline characteristics of the sample (N=1586), anti-citrullinated protein antibody (ACPA) positive and negative.

	ACPA positive (173)	ACPA negative (1413)
Mean age (standard deviation)	55.0 (7.3)	54.8 (8.0)
N (%) Female	89 (51.4)	738 (52.2)
N (%) French Canadian	111(64.1)	982 (69.5)
N (%) Never smokers	78 (45.1)	549 (38.9)
N (%) living within 2.5 km of any industrial emitter of PM2.5	66 (38.2)	560 (39.6)
N (%) living within 2.5 km of any industrial emitter of SO2	30 (17.3)	238 (16.8)
N (%) living within 7.5 km of a major industrial emitter of PM2.5	14 (8.1)	85 (6.0)
N (%) living within 7.5 km of a major industrial emitter of SO$_2$	84(48.6)	618 (43.7)

unexposed) and one continuous variable, centered to the mean exposure of those exposed (i.e. those with a value of one for the binary variable). Additional sensitivity analyses controlled for the four census metropolitan areas (Montreal, Quebec City, Sherbrooke, Saguenay–Lac-Saint-Jean) from which the subjects had been recruited.

3. Results

Among the 1586 individual CARTaGENE subjects studied in these analyses, the mean age at baseline was 55 years (SD 7.8). Just over half (N=827, 52%) were female and most (N=1,093, 69%) were French-Canadian. Almost half (43%) were past smokers, 17% were current smokers and the remainder were never-smokers. Just over 75% (1200) of the subjects came from the Montreal CMA, with 248 subjects coming from the Quebec City CMA, 75 from the Sherbrooke CMA, and 63 from Saguenay–Lac-Saint-Jean.

Among the subjects living within 7.5 km of a main emitter to PM2.5, the mean exposure was 148.4 t/year (standard deviation, SD 291.0) and among subjects living within 7.5 km of a main emitter of SO2, the mean exposure to SO2 was 197.6 (SD 834.9).

Of the 1586 subjects, 173 (10.9%) were positive for ACPA. Table 1 provides univariate comparisons between the ACPA positive and negative subjects.

Adjusted analyses (Table 2) suggested positive associations between exposure to industrial emissions and ACPA. Every 10 t increase in the sum of annual PM2.5 emissions of industries located within 2.5 km of the residence was associated with a 2% (95% CI 1–4%) increase in the odds of ACPA. Similar results were found with exposure to SO_2 emissions (with the lower confidence limit extending to the null value). As for the models where the exposures were defined by distance to a major emitter, for those living within 7.5 km of a major industrial emitter of $PM_{2.5}$, every one-km decrease from the mean distance between the residences and the closest major emitter was associated with an OR of 0.81 (95% CI 0.69, 0.96) for ACPA positivity. The same trend was also suggested with the distance from major emitters of SO_2 per km (OR 0.92; 95% CI 0.84–1.00).

We did not see strong evidence of an association between ambient residential PM2.5 levels (as estimated by satellite imagery) and ACPA.

None of the sensitivity analyses produced appreciably different results for the exposure variables.

As can be seen in Table 2, in the adjusted analyses, there were no clear evidence that age, sex, smoking, or French ancestry were independently associated with serum ACPA positivity.

4. Discussion

Genetic risk factors associated with RA are known, such as the HLA-DRB1 'shared epitope' (Huizinga et al., 2005). However, since many