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Fine particulate air pollution and systemic autoimmune rheumatic disease in two Canadian provinces

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ABSTRACT

Objective: To estimate the degree to which fine particulate (PM2.5) air pollution is associated with systemic autoimmune rheumatic diseases (SARDs).
Methods: We used population-based administrative data from Alberta (1993–2007) and Quebec (1989–2011). SARD algorithms included ≥ 2 physician billing codes, or ≥ 1 rheumatology billing code, or ≥ 1 hospitalization diagnostic code (for systemic lupus, Sjogren's Syndrome, scleroderma, polymyositis, dermatomyositis, or undifferentiated connective tissue disease). Bayesian hierarchical latent class regression models estimated the probability that any given resident was a SARD case, based on the algorithms. Mean 2001–2006 residential ambient PM2.5 levels were assigned using satellite-derived data for dissemination area regions in Alberta and CLSC regions in Quebec. The sum of individual level probabilities provided the estimated total cases per region in each province, according to age, sex, urban-versus-rural residence, income, and PM2.5 levels. In Alberta, we ran separate models for First-Nations (FN) and non-First Nations subgroups. Bayesian logistic regression modeling generated odds ratio (OR) estimates for being a SARD case, accounting concurrently for demographics, as well as an interaction term between age and sex.
Results: Our data suggested that the probability of being a SARD case was higher among females versus males and for residents aged >45 versus younger, with the highest ORs for older females. Independently, the odds of being a SARDs case increased with PM2.5 levels in both provinces.
Conclusion: Our data suggest that PM2.5 exposure may be associated with an increased risk of SARDs.

1. Introduction

Systemic autoimmune rheumatic diseases (SARDs) are complex chronic inflammatory disorders (Callaghan et al., 2007; Bernatsky

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et al., 2009; Aghdassi et al., 2011; Panopalis et al., 2007). Some SARDs include systemic lupus erythematosus (SLE), scleroderma, primary Sjogren's syndrome, and polymyositis–dermatomyositis. These conditions are characterized by an over-reactive immune system and systemic inflammation that can result in a variety of manifestations, including organ damage like kidney failure in SLE. There is compelling evidence that SARDs may be triggered by environmental factors (Cooper et al., 1999; Cooper and Stroehla, 2003; Ballestar, 2010; Shapira et al., 2010) although there remain considerable knowledge gaps.

There is a growing interest in the role of air pollution on inflammation and disease, especially particulate matter (PM). Sources of PM from human activities include road vehicles and industrial emissions. Fine PM (with a median diameter $<2.5\ \mu m$) enter the body through airways and can trigger a systemic inflammatory response. van Eeden et al. (2001) studies have linked PM to systemic inflammation, in particularly in cardiovascular disease and diabetes (Anderson et al., 2012; Chen et al., 2013). However, very few studies have examined the association between PM and SARDs. One category of PM, diesel exhaust nanoparticles, has been shown to have pro-inflammatory effects on the cells of patients with systemic autoimmune rheumatic disease (Mastrofrancesco et al., 2014). In addition preliminary data has shown an association between road-traffic density and SLE prevalence in Montreal (Labrecque et al., 2010), found links between PM2.5 levels and SLE activity in a clinical SLE cohort (Bernatsky et al., 2011a,b), and suggested PM2.5 and SO_2 industrial emissions as triggers of autoimmunity (Bernatsky et al., 2015a,b).

Our objective was to provide more information regarding the effects of pollution on SARDs prevalence in two provinces in Canada.

2. Methods

We used population-based administrative health data from the provinces of Alberta (1993–2007) and Quebec (1996–2011). In Canada, each province maintains linkable databases on all residents who are recipients of a comprehensive health plan. The databases record one physician billing diagnosis code per visit (in Alberta, up to three diagnosis codes are allowed, but infrequently used), and all hospitalizations (with up to 25 diagnostic codes per hospital separation in Alberta, and 15 in Quebec). Use of administrative data to study rheumatic disease outcomes is often done, although billing and hospitalization diagnostic codes found in administrative data are not necessarily clinically confirmed. To address this, our methods take account the imperfect nature of these diagnostic codes, using a model that calculates the sensitivity and specificity of the billing and hospitalization diagnostic codes.

We considered three algorithms that could be helpful in identifying SARD cases: ≥ 2 physician billing claims with the International Classification of Diseases (ICD)-9 code 710.x (within 2 years but at least 2 months apart); ≥ 1 such billing code by a rheumatologist; or at ≥ 1 hospitalization with an ICD-10 diagnostic code corresponding to a SARD diagnosis (M32.1, M32.8-32.9, M33-M34, M35.0, M35.8-35.9, M36.0). This includes systemic lupus erythematous, Sjogren's syndrome, scleroderma, polymyositis, dermatomyositis, and undifferentiated connective tissue disease.

The Alberta health data that we used contained the six digit postal code of the residence of the subjects. As dissemination areas are the smallest geographic areas available in the Canadian Census with socio-demographic information, the Canadian Census dissemination area associated with the residence of each Albertan subject was obtained through geographic overlay of postal code centroids on a geographic layer of the dissemination area (Statistics Canada, 2012). In Alberta, information on First Nation (FN) status is also available (Alberta Health and Wellness, 2014).

For the Quebec health file, we were only provided with the first three digits of the postal code, and the smallest geographic area that would include the polygons of the three digits postal codes and at which socio-demographic information was available was the area served by each Quebec 'local social and health service center' (CLSC). No reliable indicator of First Nations status is typically available in Quebec administrative data.

The population by age group and sex at the dissemination area level, as well as median regional income information, was obtained from the Canadian Census 2006 for Alberta (Statistics Canada, 2014). For Quebec, the demographic information used at the CLSC level was from Canadian Census data for the year 2011 (Ministère de la Santé et des Services Sociaux. Estimations de population, 2014), and median regional income information was from Canadian Census data for 2006. Mean 2001–2006 ambient fine particulate (PM2.5) levels derived from satellite imagery (Atmospheric Composition Analysis Group, 2014) were assigned to the dissemination area of each Alberta resident and the CLSC area of each Quebec resident. We linked to each DA or CLSC of residence, mean PM2.5 levels from 2001 to 2006 derived from satellite imagery by van Donkelaar et al. (2010). van Donkelaar et al. (2010) estimated PM2.5 levels with optical depth data from the MODIS (Moderate Resolution Imaging Spectroradiometer) and MISR (Multiangle Imaging Spectroradiometer) satellite instruments, and the GEOS-Chem global chemical transport model. This data is available at ⟨http://fizz.phys.dal.ca/~atmos/martin/?page_id=140⟩. Concentrations of PM2.5 (in $\mu g/m^3$) were estimated for a grid of 10 km by 10 km and the value of each grid was assigned to all DA that were found in it. In Quebec, when more than one $10\ km \times 10\ km$ cell of the PM2.5 data were intersecting the geographic area of a CLSC, a weighed mean based on the population density within these cells was computed.

Alberta and Quebec data were analyzed separately. In the first step of our analyses, Bayesian hierarchical latent class regression models were used to estimate the probability that any given resident of Alberta or Quebec was a SARD case, given the results for our three algorithms. At the first level of this model are the individual variables (age group, sex, urban versus rural residence). The only hierarchical second level variable is the intercept, which creates probabilities within each group of characteristics. Once can then considers the priors on the intercept distributions as a third level. The model estimates and adjusts for the imperfect sensitivity and specificity of the billing and hospitalization diagnostic code information (Broten et al., 2014). The individual level probabilities were summed (for all subjects who were still alive at the end of the period) to estimate the total number of cases according to groups characterized by age (dichotomized to less than or equal to 45, or older than 45 years), sex and urban-versus-rural residence.

We then used these as outcome data in multivariate hierarchical logistic regression models that estimated odds ratios (OR) for sex, urban-versus-rural location of residence (based on the postal code information that was recorded most proximal to the date of the first ICD diagnosis code for a SARD, from billing or hospitalization data), income level, and PM2.5 levels, across all regions. Statistics Canada median income values for each Alberta dissemination area and Quebec CLSC were categorized into quartiles.

The hierarchical nature of the logistic model in this final step allowed us to estimate, on the individual level, the effects on SARDs prevalence relative to age group and sex, and on a regional level, to estimate the effects of income and pollution levels on SARD prevalence rates. Around our point estimates of the ORs generated from the model, we produced 95% credible intervals (CrI).

There are no existing data regarding the shape of a function between PM2.5 exposures and SARD risk. Since we could not be certain that the relationship of our pollution exposure and outcome (in the logistic model) would be linear, PM2.5 levels were used alternatively in quartile categories or continuously (depending on the shape of the exposure versus outcome plot for each province) and also performed sensitivity analyses with dichotomous PM2.5 values. For our sensitivity analyses with dichotomous values, the cut-point was determined by a change-point model (Beckage et al., 2007) which estimated the optimal PM2.5 level dividing high from low SARDS prevalence. Change-point analysis is a powerful tool to estimate the most probable 'cut-points' in models of an exposure's effect on an outcome. When effects are not clearly linear, change-point methods can estimate, across a range of values (here, PM2.5 levels) the probabilities that the 'change' (here, higher SARDs risk) occurs at any given value.

Since previous analyses have demonstrated that the risk of SARDs appears to be different (that is, higher) in First-Nations (FN) versus non-FN Canadians (Barnabe et al., 2012), with the Alberta data, we ran two models, one within each group.

Our primary analyses used the entire period for which we had administrative data, under the assumption that the geographic variation of PM2.5 level estimates was relatively constant for the period prior to 2000 and after 2000; to check this assumption we performed sensitivity analyses specifically for 2000–2007 in Alberta.

While the administrative data included those demographic variables that were available to us, it is of course possible that variables not included (for example, pollutants other than PM2.5, or smoking) could be associated both with the outcome of SARDs and our main exposure of interest (PM2.5), causing unmeasured confounding. We thus used Bayesian methods to explore for effects of unmeasured confounders as per the methods of McCandless et al. (2007). We considered that the unmeasured confounder was present for 75% of the high exposure vs 25% for the low exposure.

3. Results

Within Alberta, there were 4127 DAs, with the average population per DA being 740 individuals (with the interquartile range across DAs being 406,722). In the Alberta administrative data, the average percentage of females, across DAs, was 50.2% (interquartile range 48.6, 51.8%), and the percentage of older individuals, across DAs, was 37.8 (interquartile range 30.8, 44.5%). Within Quebec there were 166 CLSC regions, with an average population of 48,060 residents per CLSC (interquartile range 19,480, 66,830). For Quebec, the average percentage of females was 49.9% (with the interquartile range across

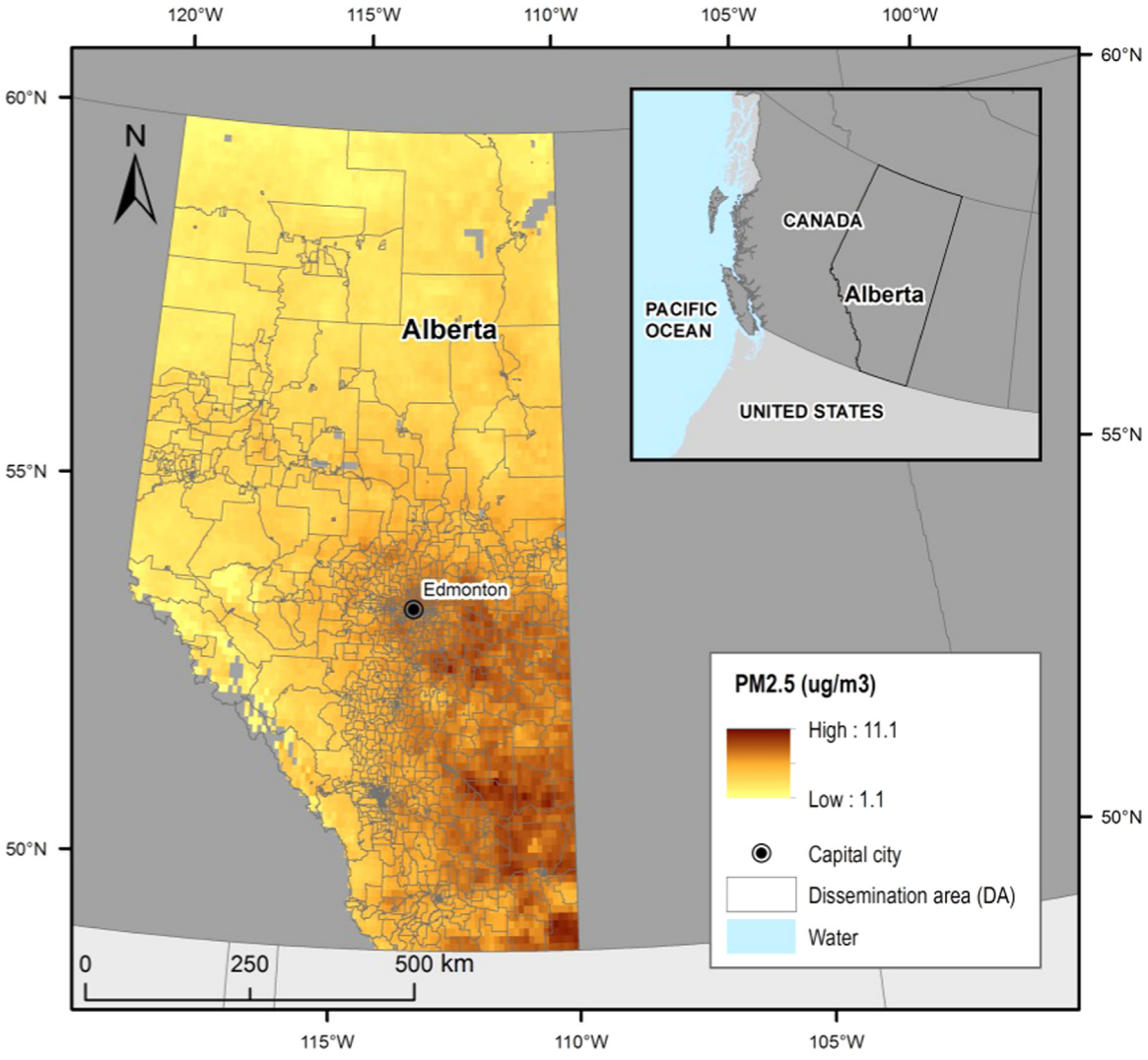

Fig. 1. Map of PM2.5 levels across Alberta.

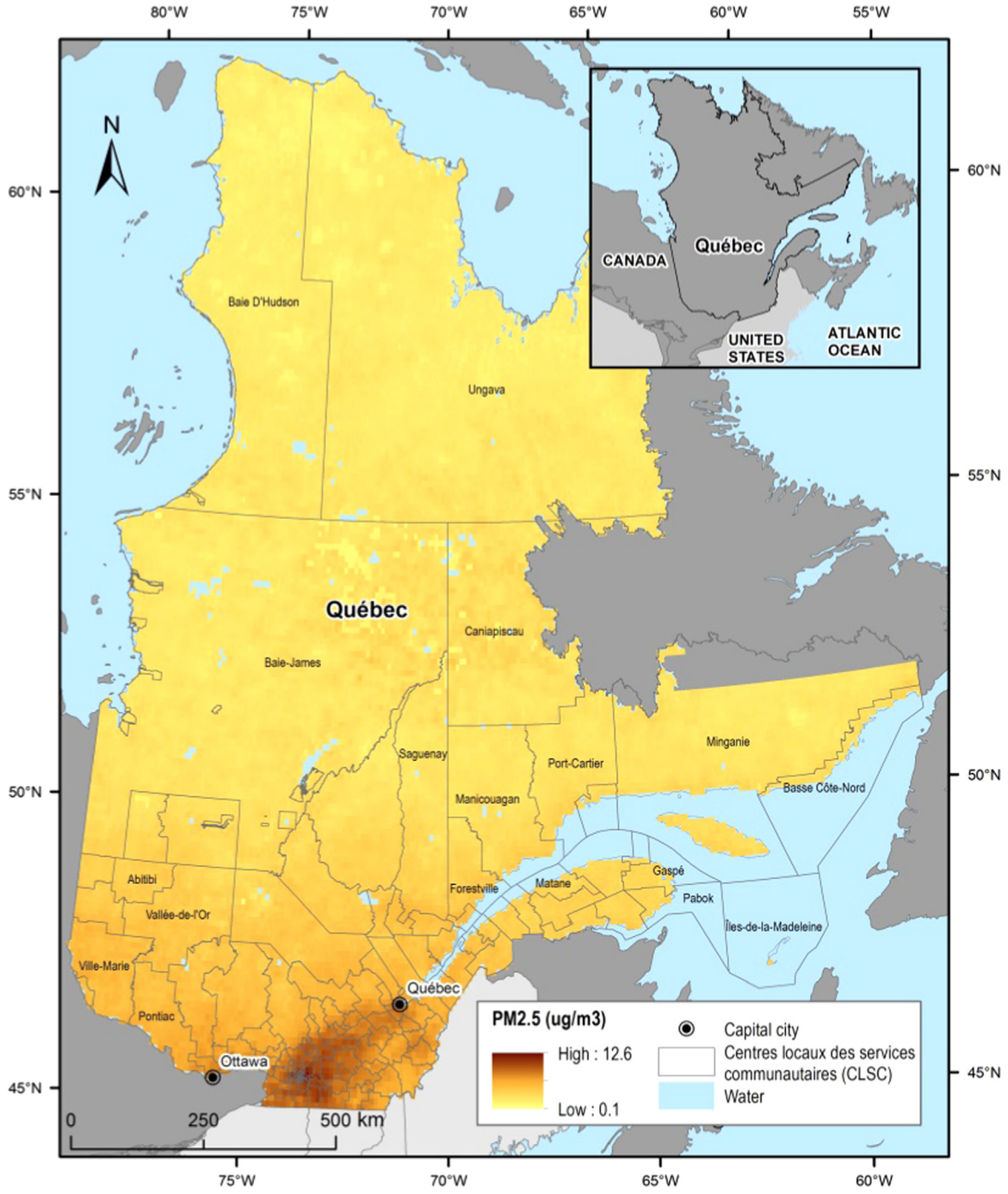

Fig. 2. Map of PM2.5 levels across local social and health service centers' (CLSCs) in Quebec.

CLSCs being 49.2, 51.0%), and the percentage of older individuals, across CLSCs, was 46.6 (interquartile range 42.2, 51.9%).

The estimated total SARD prevalence estimate in Alberta in 2011 was 2.6 cases per 1000 residents (based on an estimated 7987 non-FN and 193 FN cases among the population living in 2011) and the estimated total SARD prevalence estimate in Quebec in 2011 was 3.1 cases per 1000 residents (based on an estimated 30,330 cases among the population living in 2011). The median satellite-based PM2.5 level across DAs in Alberta was 6.9 $\mu g/m^3$ (interquartile range 6.0, 8.1) and the median satellite-based PM2.5 level across CLSCs in Quebec was 6.8 $\mu g/m^3$ (interquartile range across CLSCs 5.9, 11.6). Maps showing the distributions of PM2.5 are shown in Fig. 1 for Alberta and Fig. 2 for Quebec.

Independent of sex, age, urban versus rural residence, and median income, the odds of being a SARDs case appeared to be potentially associated with PM2.5 levels. We present the main results for Alberta (Table 1) using the exposure categories for quartiles, since there was evidence of a non-linear effect in Alberta. All explanatory variables included in the tables were included in the model simultaneously. As can be seen in Table 1, compared to the first PM2.5 quartiles, for non-FN Alberta residents, the SARDs OR point estimate was highest in the second PM2.5 exposure level quartile although this overlapped with the point estimate for the highest level. In FN Alberta residents (Table 1), the SARDs OR point estimate for the third PM2.5 level quartile (compared to the lowest quartile) was the most indicative of an effect, although the point estimate was identical for the highest PM2.5 quartile level (with a less precise CrI).

Table 1
Odds ratio (OR) estimates with the 95% credible intervals (CrI) associated with systemic autoimmune rheumatic disease in Alberta.

Non-first nations	OR	95%	CrI
PM2.5 level 6.02–6.92 μg/m^3[a]	1.25	1.15	1.36
PM2.5 level 6.93–8.11 μg/m^3	1.03	0.94	1.13
PM2.5 level ≥ 8.12 μg/m^3	1.13	1.02	1.25
Female	7.67	6.34	9.18
Older age (≥ 45 years)	5.42	4.46	6.48
Older female	26.8	22.2	32.2
Urban versus rural residence	1.10	1.02	1.19
Median income quartile 2[b]	0.99	0.92	1.07
Median income quartile 3	0.88	0.81	0.96
Median income quartile 4	0.89	0.82	0.97
First nations			
PM2.5 level 6.02–7.18 μg/m^3[a]	1.14	0.65	1.92
PM2.5 level 7.19–8.16 μg/m^3	1.77	1.02	3.13
PM2.5 level ≥ 8.17 μg/m^3	1.77	0.99	3.23
Female	7.51	4.12	15.71
Age	4.55	1.75	10.3
Older female	40.9	21.6	87.4
Urban versus rural residence	0.80	0.47	1.31
Median income quartile 2[b]	1.18	0.79	1.73
Median income quartile 3	0.99	0.63	1.53
Median income quartile 4	0.62	0.33	1.09

All explanatory variables included in the tables were included in the model simultaneously.

[a] PM2.5 = Satellite fine particulate air pollution, in μg/m^3. Levels represent increasing quartile concentrations, relative to the lowest quartile.

[b] Income median values for each Alberta dissemination area, obtained from Canadian Census data, were categorized into quartiles, given non-linear effects.

Table 2
Odds ratio (OR) estimates with the 95% credible intervals (CrI) associated with systemic autoimmune rheumatic disease in Quebec.

	OR	95%	CrI
PM2.5 level 5.09–6.79 μg/m^3[a]	0.86	0.81	0.91
PM2.5 level 6.82–11.63 μg/m^3	1.02	0.97	1.09
PM2.5 level ≥ 11.81 μg/m^3	1.45	1.36	1.56
Female	7.65	6.91	8.40
Older age (≥ 45 years)	8.24	7.44	9.10
Older female	37.2	33.7	40.9
Mixed urban and rural CLSC region[b]	1.03	0.97	1.10
Urban CLSC region	1.00	0.93	1.08
Median income quartile 2[c]	1.06	1.00	1.11
Median income quartile 3	1.02	0.97	1.07
Median income quartile 4	1.19	1.13	1.25

All explanatory variables included in the tables were included in the model simultaneously.

[a] PM2.5 = Satellite fine particulate air pollution, in μg/m^3. Levels represent increasing quartile concentrations, relative to the lowest quartile.

[b] CLSC, 'local social and health service center' regions were characterized by whether they were made up of all urban regions, or made of mixed urban and rural areas, compared to CLSC regions made of only rural areas.

[c] Income median values for each Quebec CLSC were obtained from Canadian Census data, were categorized into quartiles.

In the Quebec data, for a similar adjusted model, considering PM2.5 in quartiles, there was evidence of an increased OR for SARDs with the highest quartile (Table 2).

In our sensitivity analyses, the best estimated cut-point for the Alberta PM2.5 exposure was 5.2 μg/m^3. With PM2.5 dichotomized at this level, further sensitivity analyses using Alberta administrative data only from 2000–2007 (to better match the calendar period for which we had exposure information) were consistent with a positive relationship between PM2.5 and SARDs (OR 2.44, 95% CrI 2.32, 4.07).

We did note the data was consistent with roughly linear effects within Quebec. In Quebec, with PM2.5 as a linear variable (interpreted as the increase in SARD prevalence per 1 μg/m^3 increase in PM25), the results also suggested a positive relationship between PM2.5 levels and SARDs (OR per increase of 1 μg/m^3 1.055, 95% CI 1.049, 1.061). In our sensitivity analyses, the estimated best cut point for the Quebec satellite PM25 variable was 10.78 μg/m^3, and with this definition of the exposure the adjusted Quebec OR for the highest category of exposure was 1.49 (95% CCI 1.43, 1.53) compared to the lowest group.

Regarding the potential effects of unmeasured confounding, when we created a dichotomous variable representing an unmeasured variable that was more common for Alberta residents living in levels of higher PM2.5 compared to lower PM2.5 (75% presence of the unmeasured confounder versus 25% presence), and added this to our model of the effects of PM2.5 levels on SARDs in non-FN, we found that even if this potentially confounding variable was associated with the outcome, if its OR was less than 1.7, our results would not be substantively changed. However, if the variable was a confounder associated with the outcome with an OR of 1.7, then for the point estimate of our estimated effect of PM2.5 on SARDs, the credible interval would widen just enough to include the null value (0.99, 1.30). We found much less of a change for the same theoretical unmeasured confounder in Quebec; here we were able to run models with a theoretical confounder associated with the outcome with an OR of 3, without an important change in the estimates of the effects of PM2.5 in Quebec, suggesting that unmeasured confounding is quite unlikely to explain the PM2.5 effect in Quebec.

In Alberta, when we used a continuous variable for PM2.5, the effect appeared to be slightly greater in FN residents (adjusted OR per increase of 1 μg/m^3 1.38, 95% CrI 1.14, 1.68) versus non-FN residents (1.05, 95% CrI 1.01, 1.08 per increase of 1 μg/m^3).

4. Discussion

Our study is one of the first to ever estimate the effects of air pollution on SARD occurrence. Our population-based study makes use of a potentially very powerful resource, the comprehensive billing and hospitalization data within Quebec. We used sophisticated approaches to account for the imperfect nature of these data, and also used advanced methods to assign pollution exposures.

Though we have previously estimated SARDs prevalence in Canada (Broten et al., 2014) the evidence for a potential association of SARDs with ambient air pollution is quite novel. Besides one other paper reporting an association between exposure to PM2.5 (using land-use regression models) and SARDs within a single urban population (Calgary, Alberta) (Bernatsky et al., 2015a, b), the current work is the first to assess this outcome, and only a few studies have examined the association of particulate matter and the onset of other rheumatic diseases. In one study, PM2.5 was associated with a 60% increased risk of juvenile idiopathic arthritis in young children (Farhat et al., 2011) and in a report by Hart et al. (2009) using the Nurses' Health Study data, rheumatoid arthritis (RA) risk was up to 60% higher for subjects who lived within 50 m of a major road, versus living 200 m or farther away, suggesting that pollution emissions from road traffic may indeed be an environmental risk factor for autoimmune rheumatic diseases (Hart et al., 2009) juvenile idiopathic arthritis and RA were not diseases that we studied in the current analyses, but they are similar to the SARDs that we studied, in terms of being a rheumatic disease characterized by autoimmunity (although JIA and RA are very different clinically, from SARDs). Additionally, Hart et al. (2009) published two other relevant papers. In one, they again found that exposure to air pollutants from road vehicles (e.g. nitrogen dioxide) and to industrial emissions (e.g. sulfur dioxide) was associated with RA in a Swedish cohort (Hart et al., 2013) although other

analyses of the Nurses' Health Study data (Hart et al., 2013) failed to demonstrate these effects precisely. Interestingly, other investigators have found that RA subjects exposed to higher PM2.5 have greater levels of auto-antibodies (which correlate with RA risk and severity) (Kunkel et al., 2011).

PM can promote disease through oxidative stress mechanisms, oxygen-free radical-generating activity, DNA oxidative damage, mutagenicity, and stimulation of inflammatory cytokines. Convincing evidence from experimental models indicates that exposure to diesel exhaust and diesel exhaust particles causes oxidative DNA damage. Oxidative stress mediated by PM may arise from direct generation of reactive oxygen species (ROS) as well as activation of inflammatory cells capable of generating ROS and reactive nitrogen species (Risom et al., 2005). The smaller particles have greater ability to cause cell damage through oxidative stress and inflammation. This is likely because fine and ultrafine PM can penetrate the smallest airway components (alveoli) and be absorbed systemically.

Transition metals, ions (sulfate, nitrate), organic compounds, reactive gases, are examples of elements of PM that may be cytotoxic. The water-soluble faction of PM (i.e. transition metals that are able to provide electrons for oxidation such as iron and manganese) play important roles in membrane lipid peroxidation and oxidative DNA damage (Valavanidis et al., 2008).

Immune system cells which can be affected by PM include macrophages, which are stimulated to produce inflammatory signals, including tumor necrosis factor (TNF)-alpha, interleukin (IL)-6, and IL-1 beta (van Eeden et al., 2001). PM exposure also stimulates movement of monocytes (macrophage precursors) into tissue (Ishii et al., 2005). Moreover lymphoblasts (immune cell precursors) treated with diesel exhaust particles showed a dose-dependent response in terms of particle uptake, generation of reactive oxygen species, and induction of IL-6 and IL-8 (Vattanasit et al., 2014). These data all suggest mechanisms whereby PM could trigger risk of autoimmune diseases like SARDs, through stimulation of immune system pathways.

Use of administrative data to study rheumatic disease outcomes is increasing, although billing and hospitalization diagnostic codes found in administrative data are not necessarily clinically confirmed. To address this, our methods take account the imperfect nature of these diagnostic codes, using a model that calculates the sensitivity and specificity of the billing and hospitalization diagnostic codes (Broten et al., 2014). In previous work, we have shown the majority of identified cases within administrative data do have some type of SARD, although there is some misclassification between categories (SLE vs. scleroderma, for example) (Bernatsky et al., 2011a,b). In contrast to Quebec, Alberta allows physicians to submit more than one billing code, but among the SARD billing codes submitted in Alberta, almost 90% of them were not accompanied by another billing code.

In our earlier work, we found there was some variation in sensitivity estimates of different SARD algorithms according to province and demographic groups. As a general trend, sensitivity estimates for SARD algorithms based on billing codes tended to be much higher than sensitivity estimates for hospitalization diagnoses (which in some groups was as low as about 30%) (Broten et al., 2014). Rheumatology billing code definition sensitivity estimates tended to higher for the younger groups and the urban groups. In general, hospitalization data was the less sensitive for case detection, across provinces and demographics, compared to billing data.

A potential limitation of our work stems from the fact that in administrative data, there is no easy, accurate way to capture certain potential confounding variables, such as smoking (which could theoretically be higher or lower in regions of Alberta where PM2.5 levels were higher or lower). However, we did attempt to model the effects of unmeasured confounders. Based on this, we believe that an unmeasured variable (or set of unmeasured variables) with confounding effects would have to be associated with an OR of at least 1.7 in order to change our interpretation (that is, might change the interpretation of our results, to be less conclusive). Thus, our results appear to be robust to unmeasured confounding, up to an OR of 1.7. Although there is little published data on smoking as a risk factor for SARDs per se, the relative risk related to smoking, for developing RA is less than this (Di et al., 2014). This suggests, perhaps, that unmeasured confounding by smoking is not an important limitation to our findings. In fact, recent Canadian analyses have shown that smoking was actually *inversely* associated with PM2.5, which would suggest that, presuming smoking to be a risk factor for SARDs, any residual confounding related to smoking in our analyses would actually result in a conservative estimate of the effects of PM2.5 on SARDs (Villeneuve et al., 2011; Exposure Assessment in Occupational and Environmental Epidemiology 2003). We must also acknowledge the possibility of biases from residual spatial auto correlation (similarity of disease rates in nearby areas) not allowed for in our models.

One additional potential issue is temporality. Because we estimated PM2.5 concentrations at a single time period, our analyses are based on the assumption that the geographic variation of PM2.5 estimates was relatively constant for the study period. PM2.5 levels may have decreased or increased locally with the closure or opening of new industrial sources and other land-use changes such as expanding road networks and residential populations. However, there are currently no fine scale pollution models available for estimating historic concentrations over this entire time period. Community-level trends suggest PM2.5 levels have remained relatively constant since the late 1990s, with only a slight downward trend noted in major Canadian cities (Wood, 2012).

Another important possible limitation is due to the spatial resolution of the information used to estimate individual exposure. Errors in residential exposure occur as PM2.5 levels vary within a geographic area of $10 \times 10\ km^2$. Future work should assess associations between SARDs and more precise PM2.5 levels estimated at a smaller geographic scale. Population-based studies on the adverse effects of ambient outdoor air pollutants are always potentially subject to misclassification errors (Labrecque et al., 2010). Nonetheless, as mentioned in the introduction, our own team has shown the association between road-traffic density and SARD onset in Montreal (Bernatsky et al., 2011a,b) as well as suggested links between PM2.5 levels and SLE activity in our Montreal SLE cohort (El-Gabalawy et al., 2011).

There are several reasons why the effects in different provinces may be slightly different; Quebec is quite different from Alberta in many ways (different dominating industries, different population densities and structures, etc.) and there is no reason to expect the functional forms for PM2.5 to be the same. Moreover, because we only had 3-digit postal code information in Quebec, we had to use a different geographic area unit used for Quebec (CLSC) versus Alberta (where we used DA) and this may have influenced some aspects of our findings (for example, exposure error may have varied). Finally, the distribution of FN groups is different in the two provinces, and we were unable to model the effects of FN status within the Quebec data. It is known that FN residents in Canada may have specific genetic predispositions to systemic rheumatic diseases like RA (Newkirk et al., 2012), and currently it is believed that a combination of genetic predispositions *plus* environmental triggers are what lead to clinically manifested disease (Newkirk et al., 2012).

Emerging evidence suggests that as well as concentrations of PM2.5, the composition of PM2.5 may differ markedly across

jurisdictions, and thus certain 'types' of PM2.5 may be capable, even at relatively low concentrations, of causing health effects (through oxidative damage etc.) (Cakmak et al., 2014). This is potentially why, even at the relatively lower levels seen in developed countries like Canada (compared to very high levels found in some cities in Asia and several low-income countries (World Health Organization, 2015)), PM2.5 may still have adverse health effects.

In conclusion, our study suggested PM2.5 is associated with SARDs. Improving air quality might reduce chronic disease burden, not only for respiratory and cardiac disease, but also systemic autoimmune rheumatic diseases.

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