Systemic onset juvenile idiopathic arthritis and exposure to fine particulate air pollution

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Abstract

Objective

Fine particulate matter ($PM_{2.5}$) is a measurable component of ambient pollution, and positive associations of short-term $PM_{2.5}$ exposure with the clinical presentation of systemic onset juvenile idiopathic arthritis (SJIA) in young children have been described in a regional cohort. Our objective was to further establish associations between short-term pollution exposures and the reported clinical event of SJIA onset in cases residing from multiple metropolitan regions.

Methods

A case-crossover study design was used to analyse associations of short-term $PM_{2.5}$ exposures with the event of SJIA symptom onset from cases residing in five metropolitan regions. Time trends, seasonality, month, and weekday were controlled for by matching. Selected exposure windows (to 14 days) of $PM_{2.5}$ were examined.

Results

Positive, statistically significant associations between $PM_{2.5}$ concentrations and elevated risk of SJIA were not observed. The most positive associations of short-term $PM_{2.5}$ exposure with SJIA were in children <5.5 years (RR 1.75, 95% CI 0.85–3.62). An ad hoc extended pooled analysis including previously reported cases from Utah's metropolitan areas identified an increased risk of SJIA for children <5.5 years (RR = 1.76, 95% CI 1.07–2.89 per 10 $\mu g/m^3$ increase in 3-day lagged moving average $PM_{2.5}$).

Conclusion

In this multi-city, multi-period study small, statistically insignificant $PM_{2.5}$-SJIA associations are observed. However, as found in prior study, the $PM_{2.5}$-SJIA association is most suggestive in preschool aged children. Larger numbers of SJIA cases spatially located in geographic areas which experience a greater day to day ambient particulate burden may be required by the analysis to demonstrate effects.

Key words

systemic arthritis, juvenile idiopathic arthritis, particulate matter, environmental pollution

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Introduction

Numerous epidemiologic, time-series studies have supported the hypothesis that pulmonary mediated, systemic inflammation induced by exposure to air pollutants contributes to the development of pro-inflammatory disease, including coronary atherosclerosis and acute inflammatory mediated coronary events (1). Fine particulate matter (aerodynamic diameter less than or equal to a 2.5-μm cut point, $PM_{2.5}$) is a measurable component of ambient urban pollution. Positive associations of short-term $PM_{2.5}$ exposure with flare of a systemic pro-inflammatory response have been identified in children (2). Children are a population susceptible to inhalation exposures due to their time spent outdoors, greater activity levels, and more air inhaled per body weight and lung surface area (3).

Juvenile idiopathic arthritis (JIA) is a chronic autoimmune disease with childhood onset, involving inflammatory arthritis in one or more joints, comprised of phenotypically distinct subtypes defined by the International League of Associations for Rheumatology (ILAR) (4). Patients with systemic juvenile idiopathic arthritis (SJIA) are a distinct subtype of JIA; they initially have fever and systemic inflammation and features may include rash, lymphadenopathy, serositis, and hepatomegaly. By ILAR criteria they develop inflammatory arthritis, but in the initial stages of clinical illness their systemic inflammatory symptoms predominate.

The aetiology of SJIA is believed to be multifactorial, and both genetic and environmental influences play a pathogenic role (5). Temporal season, a likely surrogate for environmental influences, may contribute (6, 7). In a regional case-crossover study, we identified positive associations of short-term $PM_{2.5}$ with the clinical onset of JIA (8). Associations were strongest in 1) young children having SJIA, 2) male subjects, and 3) during the coldest months when the regional day-to-day ambient $PM_{2.5}$ concentration is highest and most variable. Activation of innate immune pathways is more prominent in SJIA compared with non-systemic JIA subtypes, and fine particles of ambient pollution illicit toll-like, receptor-dependent innate immune responses which may play an important role (9, 10). The objective of our study was to further establish associations between short- term ambient pollution exposures and the reported clinical event dates of SJIA onset in cases residing in multiple metropolitan regions. A case-crossover study design was used to define associations of short-term $PM_{2.5}$ exposures with the event date of SJIA symptom onset from these regions.

Methods

Study participants and event data

Our study was approved by the institutional review board of participating institutions. Cases originate from physician operated SJIA patient registries. Patients were diagnosed at the following paediatric specialty centres: The Hospital for Sick Children (Toronto), Boston Children's Hospital (Boston), Cincinnati Children's Medical Center (Cincinnati), Children's Hospital of Philadelphia (Philadelphia), and Children's Healthcare Atlanta (Atlanta). Cases have been carefully phenotyped by board certified paediatric physicians specialising in the care of children with rheumatic disease, specifically JIA. These regional datasets have previously been used in other epidemiologic and clinical research studies validating their use in our epidemiologic study (6, 11-17). Subjects for the case-crossover study met the following inclusion criteria: 1) the International League of Associations for Rheumatology (ILAR) classification criteria for SJIA or were cases provisionally diagnosed and treated for SJIA prior to having objective signs of arthritis and 2) at time of clinical disease onset (typically fever onset) the subjects resided within the metropolitan study areas. The U.S. metro areas of study were defined by Metropolitan Statistical Area (MSA) or Primary Metropolitan Statistical Area (PMSA) as defined by the U.S. Office of Management and Budget (http://www.census.gov/population/metro/files/lists/historical/99mfips.txt) and included: Atlanta, GA MSA; Boston, MA-NH PMSA; Cincinnati, OH-KY-IN PMSA; Philadelphia, PA-NJ PMSA. The Toronto metropolitan

area of study was the Census metropolitan area of Toronto, Ontario as defined by Statistics Canada (https://www12.statcan.gc.ca/census-recensement/2011/as-sa/fogs-spg/Facts-cma-eng.cfm?LANG=Eng&GK=CMA&GC=535) plus the three communities of Whitby, Oshawa, and Burlington. Baseline participant variables on individual subjects included age, gender, clinical features of SJIA at diagnosis, SJIA disease course, and pretreatment laboratory markers of inflammation (C-reactive protein).

Pollution and weather data

For the four U.S. cities, daily PM2.5 concentration data were gathered from the U.S. Environmental Protection Agency (EPA) Air Quality System (AQS) (http:// www.epa.gov/ttn/airs/aqsdatamart/). For Toronto, $PM_{2.5}$ data were collected from the Ontario Ministry of the Environment (http:// www.airqualityontario.com/history/). For each city, we chose a central monitoring site. This choice was based on central location in the metropolitan area and availability of a comprehensive collection of daily $PM_{2.5}$ concentrations. We also collected data from other available sites in the metropolitan area. For each city, daily $PM_{2.5}$ concentration data from the central site was regressed on the data collected from surrounding sites. $PM_{2.5}$ concentrations across cities were highly correlated (R^2 values between 0.78 and 0.95). Missing daily $PM_{2.5}$ concentrations at the central site were imputed by using the regression results and the $PM_{2.5}$ concentrations at the nearest available $PM_{2.5}$ monitor. Weather data for all cities were collected from the National Climatic Data Center (http://cdo.ncdc.noaa.gov/cgi-bin/cdo/cdostnsearch.pl).

Statistical analysis

Analysis of SJIA cases were based on a case-crossover design, which is a modification of the case-control design. This approach matches exposure at the time or shortly before the event with other time periods for which the event did not occur (control or referent periods) and evaluates potential excess risk using conditional logistic regression. Because patients serve as their own controls, there is near-perfect matching on all participant-specific attributes that do not change over time. In this analysis, referent exposure periods were matched on day of week in the same month and year as the reported onset date of SJIA, resulting in either 3 or 4 referent periods for each patient. By choosing these matching referent periods, time-dependent risk factors such as day of week, seasonality, and long-term time trends are controlled for by design. Details concerning the use of conditional logistic regression in case-crossover design can be found elsewhere (18, 19). We conducted pooled analyses where observations for all cities were combined. Analyses were stratified by individual city, gender, age, and disease characteristics. We also conducted analyses using only observations where pollution data were available at the central site data and with observations that also included imputed data. $PM_{2.5}$ concentrations for different lag structures, including concurrent day, previous day, and lagged moving average concentrations ≤14 days were evaluated. We also conducted the analysis controlling for weather variables, including the control of concurrent day temperature and dew point temperature (as both linear and quadratic terms).

In addition, for comparison and confirmation purposes and to enhance the overall statistical power, we conducted an ad hoc extended pooled analysis where we also included the 29 SJIA events that were collected and used in the previously reported study from Ogden, Salt Lake City, and Provo/Orem metro areas of Utah. For this extended pooled analysis we used the imputed $PM_{2.5}$ exposure data and event data (from 1993–2006) as previously documented (8).

Results

The years for which $PM_{2.5}$ data was collected included 1999–2013 for all metro areas except Toronto, where only data from 2003–2013 were collected (Table I). Each of the metropolitan areas had one or more alternate monitors that allowed for imputations of $PM_{2.5}$ values on the central site when data were missing. $PM_{2.5}$ concentrations were highly correlated between central site and alternate sites (R^2 values between 0.78 and 0.95). $PM_{2.5}$ concentration means (and SD) were nearly identical for observations using only the central site data and for observations using central site data plus values imputed from alternate monitors.

Of 253 total SJIA cases, over 40% of the patients resided outside of the metropolitan areas at their reported date of clinical onset. Of the 144 observations in the metropolitan areas, dates of known onset within a 2-week window, 7-day window, or 2-day window were available for 114, 97, and 76 subjects, respectively. The actual number of events used in each conditional logistic regression (N) depends on availability

Table I. $PM_{2.5}$ monitored and imputed concentration means (and SD) for all study metro areas.

City	Years with $PM_{2.5}$ data	No. days with $PM_{2.5}$ data	Mean $PM_{2.5}$ µg/m^3	SD	No. alternative monitors to impute $PM_{2.5}$	R^2 values between central and alternative monitors
Atlanta, central site	1999-2013	4517	15.0	7.8		
Atlanta, central site plus imputed		4782	14.8	7.7	2	0.85, 0.85
Boston, central site	1999-2013	2447	10.8	6.6		
Boston, central site plus imputed		4906	9.8	5.7	3	0.78-0.84
Cincinnati, central site	1999-2013	3140	16.5	8.3		
Cincinnati, central site plus imputed		3806	16.4	8.1	3	0.89-0.95
Philadelphia, central site	1999-2013	4082	13.3	8.3		
Philadelphia, central site plus imputed		5249	13.0	8.1	4	0.93-0.95
Toronto, central site	2003-2013	3998	7.0	6.0		
Toronto, central site plus imputed		4018	7.1	6.0	1	0.91

Table II. Number of observations and estimated RR (95% CI) of an onset of SJIA associated with an increase of 10 μg/m^3 $PM_{2.5}$ lagged moving average concentration of the 3 and 7 day lagged exposure period for all observations within the study metro areas (Philadelphia, Cincinnati, Atlanta, Boston, and Toronto).

	Number of Observations	RR (95% CI)	
		3-day MA	7-day MA
Total Observations	253	0.859 (0.645-1.144)	0.928 (0.634-1.356)
Total in Metro Areas	144	0.892 (0.599-1.330)	0.888 (0.532-1.482)
Metro Area observations with onset time estimated within 2-week window	114	0.944 (0.606-1.471)	1.000 (0.574-1.744)
Metro Area observations with onset time estimated within 7-day window	97	1.022 (0.634-1.647)	1.018 (0.555-1.866)
Metro Area observations with onset time estimated within 2-day window	76	1.391 (0.817-2.368)	1.410 (0.707-2.810)

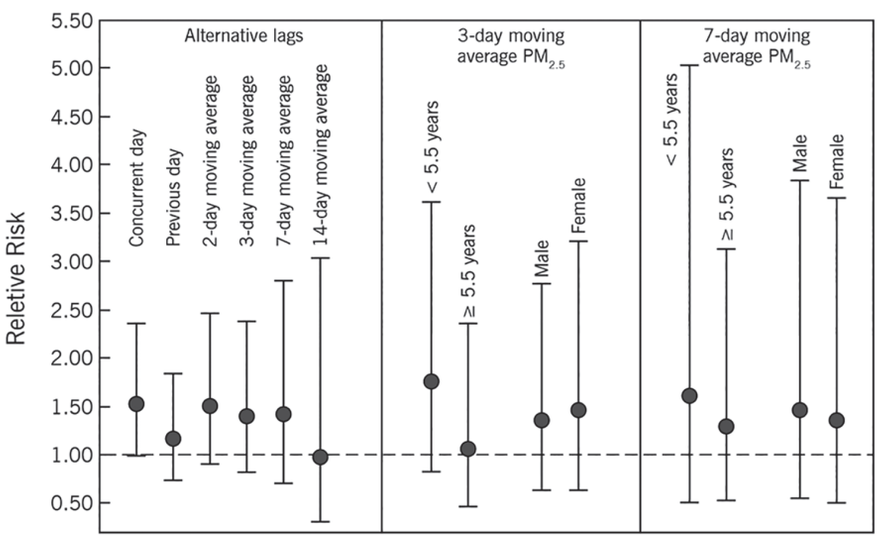

Fig. 1. Relative risks (and 95% CIs) of onset event of SJIA associated with an increase of 10 μg/m^3 of $PM_{2.5}$ using pooled and alternative lag structure for exposures using data from the central monitor plus imputed from nearby sites.

of $PM_{2.5}$ data in each city. Observations and estimated RR (95% CI) were calculated with onset of SJIA associated with an increase of 10 μg/m^3 $PM_{2.5}$ lagged moving average concentration of the concurrent and graduated lagged exposure periods up to 14 days for all observations within the pollution exposed metropolitan areas of Philadelphia, Cincinnati, Atlanta, Boston, and Toronto. Table II presents the observations and estimated RR (95% CI) of an onset of SJIA associated with an increase of 10 μg/m^3 $PM_{2.5}$ lagged moving average concentration of the 3 and 7-day lagged exposure period (concurrent and preceding) for all observations within the examined pollution exposed metropolitan areas. There is no consistent, statistically significant, positive correlation between increased short term $PM_{2.5}$ exposure and elevated SJIA onset risk. For the subgroup of cases with onset date limited to within a 2-day interval, associations are positive but remain statistically insignificant.

Figure 1 illustrates the relative risk estimates (and 95% CIs) of onset of SJIA associated with 10 μg/m^3 of $PM_{2.5}$ using pooled events with an estimated onset time window of 2-days but with alternative lagged exposure periods (including concurrent day, previous day, and lagged moving averages of 2 to 14 days). Results were nearly identical when the analysis was controlled for weather variables, including the control of concurrent day temperature and dew point temperature as both linear and quadratic terms (results not shown). The effect estimates are highly insensitive to the inclusion of observations with imputed $PM_{2.5}$ data and controlling for the weather variables, and positive, statistically significant associations between $PM_{2.5}$ concentrations and elevated risk of SJIA onset are not observed. Extended analysis with stratification by gender and age (<5.5 and >5.5 years) were performed. The most positive, but still statistically insignificant, associations of short-term $PM_{2.5}$ exposure with the reported clinical onset of SJIA were in young children, less than 5.5 years of age (RR 1.75, 95% CI 0.85–3.62). Stratification by metropolitan area, ILAR criteria, documented onset of systemic symptoms (fever), signs (lymphadenopathy, hepatosplenomegaly, serositis), and laboratory features (CRP) provided no statistically significant associations or differences across strata, but this analysis was limited by missing data on disease specific features in individual subjects. Analysis was also conducted using all SJIA cases, including those outside of the metropolitan area and/or with the exact date unknown. These stratified analyses also provide no evidence of a consistent, statistically significant, positive association between elevated exposure to $PM_{2.5}$ and elevated risk of SJIA onset for any of the strata.

Figure 2 presents results where the 29 SJIA events that were collected and used in the previously reported study from Ogden, Salt Lake City, and Provo/ Orem metropolitan areas of Utah were also included. This ad hoc extended pooled analysis further confirms the lack of a statistically significant positive association between the pooled SJIA events and elevated $PM_{2.5}$ for any of the exposure lag structures. However, based on the stratified results by age, there is a statistically significant increased risk of SJIA for children less than 5.5 years of age (RR=1.76, 95% CI 1.07–2.89 per 10 μg/m^3 increase in 3-day lagged moving average of $PM_{2.5}$).

Discussion

Epidemiology studies have examined whether long term exposures to air pollutants as measured by ambient par-

ticulate and gasseous pollutant concentrations and by distance to high density traffic roadways were associated with the risk of acquiring a diagnosis of rheumatoid arthritis (20–23). Our preliminary work identified positive associations between the symptom onset of SJIA in young children with short-term $PM_{2.5}$ concentrations indicative of the Salt Lake City region's pollution episodes (8). That case-crossover study was conducted in the urban Wasatch mountain valley of Salt Lake City, Utah where the concentrations and day-to-day variability of $PM_{2.5}$ are among the highest in the United States (24). Associations were strongest for SJIA events in the relatively young children (ages <5.5 years). Despite having low study numbers, the effect estimates were relatively large compared to estimates of PM effects on cardiopulmonary deaths or ischemic heart disease (25-29). The focus of the present study was to reexamine the effect of short-term $PM_{2.5}$ on SJIA in a multi-city approach.

This analysis does not reveal statistically significant associations between elevated exposure to $PM_{2.5}$ and elevated risk of SJIA generally, however the results certainly are not compellingly null. When we focus on observations with spatial specificity (*i.e.* in the well-defined metropolitan areas) and with temporal specificity *i.e.* with more accurate onset dates), the association with $PM_{2.5}$ is more positive but remains statistically insignificant. Of these more spatially and temporally defined cases, more positive but still statistically insignificant associations of short-term $PM_{2.5}$ exposure with SJIA onset were found in young children, less than 5.5 years of age (lagged moving average 3 days: RR 1.75, 95% CI 0.85–3.62). Preschool age was the chosen categorical age cut off, since in the metropolitan region of Salt Lake City significant associations were found in this age group between average pollution concentrations 14 days prior to the event and JIA onset, and the pollution-related excess risk for SJIA was relatively large (lagged moving average 14 days: RR=3.77, 95% CI 0.89–16.00) (8).

Our study has several strengths. Since SJIA is clinically defined by its onset of symptoms in the acute disease period, it is an appropriate disease to study using the case-crossover study design which requires a defined event date, *i.e.* date of fever/symptom onset. This is not typical of the majority of rheumatologic diseases, which often have an indolent course, making directed exposure assessment prior to clinical onset challenging. Our multi-city study included a larger number of SJIA cases than we had studied previously in Utah's urban Wasatch front. Also, cases were identified by direct physician assessment rather than a surrogate of disease diagnosis and date of onset, such as discharge code and initial hospital admission date (30). All cases were well phenotyped patient subjects within existing databases, run by board certified, paediatric physicians specialising in the care of children with rheumatic disease. Cases from these databases have been used in numerous other studies including epidemiologic studies (6, 11-17). Our study also 1) includes different geographical metropolitan areas of exposure with differences in the regional composition of particulate exposures; 2) uses the case-crossover design which controls for cross subject-differences that do not vary over time; and 3) controls by matching for weekday, month, time trends, and seasonality.

The number of primary cases remains low, even though cases reside within multiple cities with major tertiary care paediatric referral centres for rheumatic disease spanning over a decade. In order to add observations and enhance overall statistical power – albeit in an ad hoc fashion – we conducted an extended pooled analysis where we also included the 29 SJIA events that were collected and used in the previously reported study from Ogden, Salt Lake City, and Provo/Orem metro areas of Utah. This analysis found even less evidence of an overall statistically significant positive association between pooled SJIA events and elevated $PM_{2.5}$. However, the original analysis observed a positive $PM_{2.5}$-SJIA association for young children, as does the current analysis. When the results are pooled, there is actually a statistically significant increased risk of SJIA for children less than 5.5 years of age for some exposure lag structures. While not compelling, these results remain suggestive.

Unlike large, coarse particles, fine particles enter small airways stimulating short-term pulmonary and systemic inflammatory responses, involving stimulated macrophage release of pro-inflammatory cytokines (31). Translational studies and medication trials have identified the importance of IL-1 and IL-6 in the initial systemic phase of SJIA; also, prior to treatment SJIA patients in the systemic phase have peripheral blood mononuclear cell gene

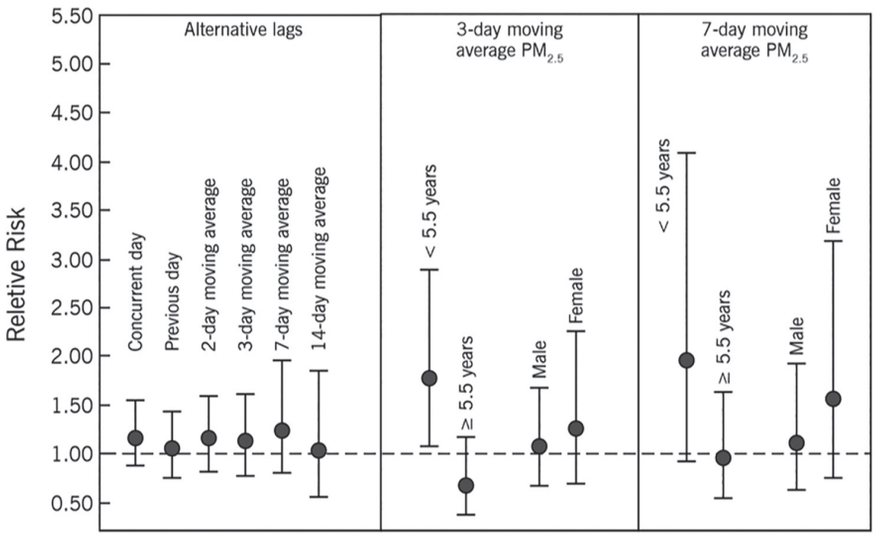

Fig. 2. Relative risks (and 95% CIs) of onset event of SJIA associated with an increase of 10 μg/m^3 of $PM_{2.5}$ using pooled data – plus SJIA events from Utah previously reported – and alternative lag structure for exposures using data from the central monitor plus imputed from nearby sites.

expression profiles exhibiting greater activation of innate immune pathways IL-6 and toll-like receptor/IL-1 receptor compared with non systemic onset JIA patients (5, 9). Fine particles are understood to illicit toll-like receptor-dependent innate immune responses suggesting a plausible mechanism for the triggering role of fine particles in the inflammatory response of SJIA patients (10).

Another limitation of the study design is the examination of only short-term acute exposure (exposure periods of 1 day to 2 weeks) and its potential to trigger clinical onset of disease events. There is evidence that long-term, repeated exposure to elevated concentrations of $PM_{2.5}$ contributes to 1) oxidative stress, 2) low to moderate grade inflammation, and 3) the progression of autoimmune disease (32, 33). If the relevant window of pollution exposure is substantially longer than a week or so, this study design is unable to fully capture pollution effects. Systemic JIA patients over time often develop chronic arthritis, a characteristic autoimmune disease feature, suggesting a pathogenic role played by synergistic, chronic inhalation exposures such as cumulative ambient particulates, silica, and second hand cigarette smoke involving oxidative stress, reactive oxygen species, and polyclonal T cell activation (34, 35). Also, over time recurrent infection may play an immunopathogenic role (36). It would be interesting to examine whether short-term $PM_{2.5}$ exposure correlates with SJIA subtype (monophasic, chronic inflammatory, with chronic arthritis); however, we were unable to stratify the analysis by SJIA subtype due to the lack of consistent case data across centres.

Furthermore, the reported date of fever onset may not accurately represent the date from which environmentally mediated short term inhalation exposures initially trigger inflammatory disease pathogeneses in SJIA, resulting in imperfect matching of exposure and onset. Also, the pollution measures have been collected from fixed-site outdoor monitors and do not measure potential short-term changes in concentrations of indoor air or account for important short-term personal exposures, such as those from second hand tobacco smoke. There is not full spatial resolution regarding location of cases to fully account for specific sites of high PM emission such as industrial sites; however, we have previously shown that at least within the urban region of Salt Lake City the effect of chronic PM exposure on the presentation of JIA is not dependent on residential distance to sites of high PM emission including industrial sites (37). Importantly, over 40% of the 253 cases resided outside of the metropolitan areas in environments with low day-to-day fine ambient particular exposures, exposing the fact that onset of SJIA is not dependant on the triggering effects of ambient urban air pollution exposures.

Prior research has shown that short-term exposure to fine particulate air pollution has contributed to cardiorespiratory disease exacerbations, and this study is an important follow-up investigation of the potential effects of short-term exposure to particulate pollution on systemic juvenile idiopathic arthritis clinical disease onset. The results reported in this paper are similar to our prior published results, and when data from our previous work is combined with this analysis, there is suggestive evidence of a $PM_{2.5}$-SJIA association in preschool aged children supporting the hypothesis that short-term exposure to air pollution contributes to the risk of SJIA. However, despite our multi-city, multi-period study approach, this study remains underpowered to make convincing statistical inferences. Further research with larger numbers of SJIA cases and in geographic areas which experience a greater ambient particulate burden is a suggested next step.

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