Juvenile idiopathic arthritis and exposure to fine particulate air pollution

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Abstract

Objectives

Inhalation of fine particulate matter, including particles with an aerodynamic diameter less than or equal to a 2.5-μm cut point ($PM_{2.5}$), has been associated with systemic inflammation and the clinical presentation of various cardiopulmonary heath events. The urban area along Utah's Wasatch Mountains has high $PM_{2.5}$ concentrations during periods of stagnant air conditions. Short-term inhalation exposures may trigger inflammatory events presenting as symptom onset in new patients with juvenile idiopathic arthritis (JIA). This study evaluated potential associations between JIA symptom onset and temporal changes in regional air pollution measured by stagnant air conditions and $PM_{2.5}$ concentrations.

Methods

A case-crossover design was used to analyze associations of regional ambient $PM_{2.5}$ concentrations with onset date of 338 JIA cases living on Utah's Wasatch Front. Patients were drawn from the Intermountain States Database of Childhood Rheumatic Diseases (1993-2006). Time trends, seasonality, month, and weekday were controlled for by matching. Selected exposure windows of $PM_{2.5}$ and stagnant air days were used in the model to determine the effect of short term cumulative exposure on JIA symptom onset.

Results

Increased concentrations of $PM_{2.5}$ and stagnant air conditions in the preceding 14 days were associated with significantly elevated risk of JIA onset in preschool aged children (RR=1.60, 95% CI 1.00–2.54) but not older children. Elevated risk was larger in males and in systemic onset JIA.

Conclusions

Exposure to stagnant polluted air may be an environmental risk factor for JIA in young children, potentially triggered by pollution-induced pulmonary mediated inflammation.

Key words

Particulate matter, exposure, juvenile idiopathic arthritis, environment.

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Introduction

Juvenile idiopathic arthritis (JIA) is a heterogeneous collection of chronic childhood arthropathies of unknown etiology. Twin studies indicate that the concordance rate of JIA in monozygotic twin sets ranges between 25% and 40% (1) suggesting a substantial environmental influence towards JIA susceptibility. As in adult onset rheumatoid arthritis (RA), environmental agents are thought to interact with genetic factors that influence susceptibility prior to JIA onset. This interaction may trigger immunologic events that result in the clinical signs and symptoms of these chronic arthritic conditions (2).

Individuals with self reported occupational and recreational inhalation exposures, specifically to ambient silica and mineral dusts, are at increased risk of developing RA (3, 4). Smoking exposures have been associated with developing RA, most strongly in seropositive RA patients with cyclic citrullinated peptide (CCP) antibodies (5, 6). Compared with well children, children diagnosed with RA have reported higher frequencies of passive smoke exposure in their homes (7). These data come from a study designed to determine the prevalence and source of passive smoke exposure in children with chronic respiratory diseases compared with well children and children with RA. However, other studies exploring effects of inhalation exposures and JIA have not been previously conducted.

An etiologic RA model has been described by Klareskog, who has studied the role of environmental influences, particularly smoking, on the development of RA in susceptible individuals (8). In this model chronic smoking or other environmental agents are believed to stimulate pre-existing autoantibody production in genetically susceptible individuals. Later, short-term environmental triggers provide immune or pro-inflammatory stimulae to trigger an already defined immune process, precipitating the onset of clinically defined arthritis. In support of this model, exposure to second hand tobacco smoke has been shown to be associated with the presence of rheumatoid factor in arthritis free children (9). Also, a recent study has shown RA clinical disease activity is higher among active smokers compared with patients who had stopped smoking (10). It is possible that inhalation exposures trigger specific immune reactions which are important in both early disease pathogenesis and in the clinical presentation of JIA.

Air pollution, like cigarette smoke, is a complex mixture of physical properties and chemical composition, an aerosol with a particulate phase. As early as 1995 Seaton hypothesized that inhalation of ambient fine particulate matter provokes alveolar inflammation, releasing mediators in susceptible individuals (11). Since then, the majority of health effects associated with particulate matter inhalation exposures have been associated with fine particulate matter consisting of particles with an aerodynamic diameter less than or equal to a 2.5-μm cut point ($PM_{2.5}$). Sources of $PM_{2.5}$ are common and include fossil fuels combustion, vehicle and industrial emissions, and other local sources.

There is evidence of a role for pollution related pulmonary and systemic oxidative stress and inflammation, and $PM_{2.5}$ inhalation has been shown to stimulate alveolar macrophages, creating a nidus for the development of an acute systemic inflammatory response (12, 13). Even healthy children in Mexico City exposed to ambient PM have elevated serum IL-6 and TNF-α concentrations compared to controls living in regions with less pollution (14). Associations between fine particulate exposure and myocardial ischemic events, stroke, and cardiopulmonary deaths have been reported in many daily time-series studies (15, 16). In our urban region, exposure to ambient $PM_{2.5}$ is associated with myocardial infarction and with congestive heart failure episodes and exacerbations requiring hospital admission (17, 18). The prevalence of RA may be higher in urban compared with rural areas (19, 20). Potentially inhaled $PM_{2.5}$ from urban environments is a short term pro-inflammatory environmental trigger which aids in precipitating symptomatic onset in JIA.

The objective of this study is to evaluate associations between the symptom onset of JIA with both regional ambi-

ent $PM_{2.5}$ concentrations and stagnant air conditions indicative of our regional ambient pollution episodes. Because onset of symptoms likely follow a period of cumulative exposure, a distributed lag structure relating exposure to reported symptom onset date of a few days or more is hypothesized.

Methods

Study area and participants

Over two million people, approximately 80% of Utah's population, reside on a relatively narrow strip of land that fronts the west side of the Wasatch mountain range. The Wasatch Front is approximately 10 to 15 miles wide from east to west and approximately 80 miles long from north to south with three nearly contiguous metropolitan areas: the Salt Lake City area located in the center, the Ogden area to the north, and the Provo/Orem area to the south.

Participants in this study were identified from the Intermountain States Database of Childhood Rheumatic Diseases (ISDCRD). The ISDCRD is a comprehensive database at the University of Utah with clinical and demographic data on children with rheumatologic conditions including JIA (21, 22). Demographic and clinical data were collected by questionnaire and by examination of patients in the pediatric rheumatology clinics at the University of Utah, the sole regional pediatric rheumatology referral center for the Wasatch Front. Potential cases were classified as JIA according to International League of Associations for Rheumatology (ILAR) criteria (23). Only JIA patients who resided on the Wasatch Front from 1993–2006 at the time of reported symptom onset were included. Symptom onset dates were extracted from retrospective review of initial patent histories. If this date was not clearly identifiable to the day of month, but the time of month was known, it was estimated to the first or fifteenth of the month. Isolated cases with an unidentifiable symptom onset date were excluded from the sample.

Weather and pollution data

Common weather patterns are shared across Wasatch Front communities. PM concentrations become elevated during low-level temperature inversion episodes when local emissions are trapped in a stagnant air mass near the valley floor. Daily weather data from January 1, 1993 through December 31, 2006, including temperature, dew point temperature, and the clearing index were collected from the National Weather Service (Salt Lake City International Airport station). The clearing index ranges from 0 to 1050. Low index values reflect stagnant air conditions; high values reflect greater diffusion pollution potential.

Particulate air pollution data for particles with an aerodynamic diameter less than or equal to a 10 μm cut point (PM_{10}), and particles with an aerodynamic diameter less than or equal to a 2.5 μm cut point ($PM_{2.5}$) were obtained from the Utah Department of Environmental Quality, Division of Air Quality (Salt Lake City, Utah). Monitoring was conducted in accordance with the U.S. Environmental Protection Agency federal reference method (24). Data from monitoring sites along the Wasatch Front from January 1, 1993 to December 31, 2006 were collected. Three observations of extremely high PM_{10} concentrations due to extreme wind storms were deleted. In Ogden and Provo/Orem, PM_{10} monitoring was conducted at a single community-based site with monitoring completeness of 83% and 93%, respectively. In Salt Lake City, the centrally located community-based monitor (SLC AMC) was replaced by monitoring at another site (SLC Hawthorne) with concurrent overlapping monitoring for over a year. Daily PM_{10} data were available from one or more of these two sites for 95% of the days. In addition, PM_{10} data were collected from another Salt Lake City monitoring site (SLC North). Daily PM_{10} concentrations between all of the Wasatch Front sites were highly correlated (r=.72-.94). PM_{10} concentration ratios between monitors were calculated using no intercept regression models and missing values were estimated based on this ratio and monitored PM_{10} data at the nearest monitoring site with non missing data. For $PM_{2.5,}$ daily monitoring at the SLC Hawthorn and Lindon sites and every third day monitoring at the Ogden site began in January 1998. Missing values for $PM_{2.5}$ at specific monitors were estimated using available PM_{10} and clearing index data using a two-stage statistical approach reported in more detail elsewhere (17). First, PM_{10} concentration ratios between monitors were calculated using no intercept regression models and missing values were estimated based on this ratio and monitored PM_{10} data at the nearest monitoring site with non missing data. Second, for each of the three Wasatch Front metropolitan areas, the $PM_{2.5}/PM_{10}$ ratios were estimated for 10 different levels of air stagnation (CI <=100; 101-200; 201-500, 501-999; 1000-1050) and two seasonal periods (winter months, December–February, versus non winter months) using regression models and missing $PM_{2.5}$ concentrations were estimated based on these ratios.

Statistical analysis

The primary outcome variable was JIA onset and the primary exposure variable was $PM_{2.5}$. This analysis uses the case-crossover design, which is an adaptation of the retrospective case-control design (17, 25, 26). This approach matches exposures at the time of or shortly before the event of interest with one or more periods when the event did not occur (control or referent periods) and evaluates potential excess risk using conditional logistic regression. Details of the use of conditional logistic regression in case-crossover studies with application to air pollution exposure are given elsewhere (27, 28). Because JIA patients serve as their own controls, there is perfect matching on all participant-specific characteristics that do not vary over time; thus, this approach controls for participant-specific risk factors by design. By choosing matching referent periods close in time (before and after the event) and on the same day of the week, the analysis is structured such that time-dependent risk factors including day of week, seasonality, and long-term time trends are also controlled for by design. In this analysis, referent or control period exposures were matched on day of week in the same month and year as the JIA

onset event, resulting in up to four control periods per onset event. The details of this specific time-stratified referent selection approach, and a statistical exposition on why it allows for unbiased conditional logistic regression estimates and avoids bias that can occur due to time trends in exposure is presented elsewhere (27, 28).

Analyses stratified by age, gender, and ILAR JIA classifications and restricted to only the coldest six months were conducted. $PM_{2.5}$ concentrations for different exposure windows, including concurrent day and lagged moving average concentrations for exposure periods for up to 21 days (including the concurrent day) were evaluated. Sensitivity of the results to controlling for weather variables was evaluated by adding temperature, dew point temperature, and barometric pressure as linear and quadratic terms in the conditional logistic regression model. Additionally, weather indicators of air stagnation were included in the model, replacing $PM_{2.5}$ concentrations as the exposure variable.

Institutional review board approval was obtained from the University of Utah (Salt Lake City, UT).

Results

Means and standard deviations of the $PM_{2.5}$ concentrations are provided in Table I. Three hundred and seventy six JIA patients were identified who met study inclusion criteria. Thirty-eight potential subjects (38/376; 10%) met inclusion criteria, but were excluded because they had a poorly identifiable date of symptom onset. Table II presents the number of JIA onset events for various sub groups including JIA classifications. Of the 338 total events, 47% were pre-school aged (0-5.5 years), and 63% were female. Table II also presents the estimated relative risks (and 95% confidence intervals) for an onset event of JIA associated with a 10 $\mu g/m^3$ $PM_{2.5}$ lagged moving average concentration of the 14 day lagged exposure period (concurrent day and preceding 13 days) for all ages, preschool ages, by various subgroups.

Significant associations between average pollution concentrations 14 days prior to the event and excess risk of JIA onset were observed for preschool aged children, but not for children 6 years of age or older. The pollution-related excess risk was larger when observations with the onset day of month were not 1 or 15. The estimated pollution-related excess risk was also larger when only events that occurred in the coldest 6 months (October–March) were included. When restricted to preschool aged children, only cold months, and only events that did not occur on the 1st or 15th, there were only 30 events. Yet the pollution-related excess risk was statistically significant (p=0.014) and relatively large. Remarkably, although there were only 16 onset events for preschool aged children, and the pollution-related excess risk was not statistically significant (p=0.072), the pollution-related excess risk for systemic onset JIA was relatively large

Table I. Summary of pollution concentration data (1993-2006).

Monitoring Sites		N (days)	Mean	SD
Ogden	$PM_{2.5}$ monitored	1005	10.6	9.9
Ogden	$PM_{2.5}$ monitored + imputed	5108	10.7	9.3
SLC, Hawthorne	$PM_{2.5}$ monitored	3007	11.1	11.2
SLC, Hawthorne	$PM_{2.5}$ monitored + imputed	5109	11.9	11.8
Provo/Orem, Lindon	$PM_{2.5}$ monitored	3021	10.1	9.3
Provo/Orem, Lindon	$PM_{2.5}$ monitored + imputed	5113	10.6	10.7

$PM_{2.5}$ refers to particles with an aerodynamic diameter less than or equal to a 2.5 μm cut point.

Table II. Relative risks (and 95% confidence intervals) of an onset event of juvenile idiopathic arthritis associated with an increase of 10 $\mu g/m^3$ $PM_{2.5}$ lagged moving average of 14 days for all ages, preschool ages, and various subgroups.

	All Ages (0 – 16.5)		Pres-school (0 – 5.5 yrs)	
	No. Events	RR (95% CI)	No. Events	RR (95% CI)
All Obs.	338	1.11 (0.85-1.45)	159	1.60 (1.00-2.54)**
Exclude obs. with onset day 1, 15	119	1.33 (0.85-2.09)	61	2.33 (1.09-5.00)**
Coldest 6 months (Oct .– March)	154	1.14 (0.87-1.50)	73	1.76 (1.08-2.87)**
Coldest 6 months (Oct .– March) & exclude obs. with onset day 1, 15	57	1.37 (0.87-2.17)	30	2.78 (1.23-6.29)**
Female only	213	1.11 (0.79-1.56)	106	1.25 (0.71-2.21)
Male only	125	1.10 (0.72-1.69)	53	2.62 (1.11-6.18)**
JIA 1 (Systemic onset)	29	1.06 (0.53-2.11)	16	3.77 (0.89-16.00)*
JIA 2 (Polyarticular RF+)	25	0.75 (0.25-2.29)	1	---
JIA 3 (Polyarticular RF-)	62	1.55 (0.72-3.32)	27	1.59 (0.46-5.44)
JIA 4 (Oligoarticular)	167	1.23 (0.83-1.84)	108	1.34 (0.75-2.39)
JIA 5 (Enthesitis related)	39	0.84 (0.38-1.86)	3	---
JIA 6 (Psoriatic)	4	---	1	---
JIA 7 (Undifferentiated)	12	0.88 (0.34-2.31)	3	---

**indicates p<0.05.
*indicates p<0.10.

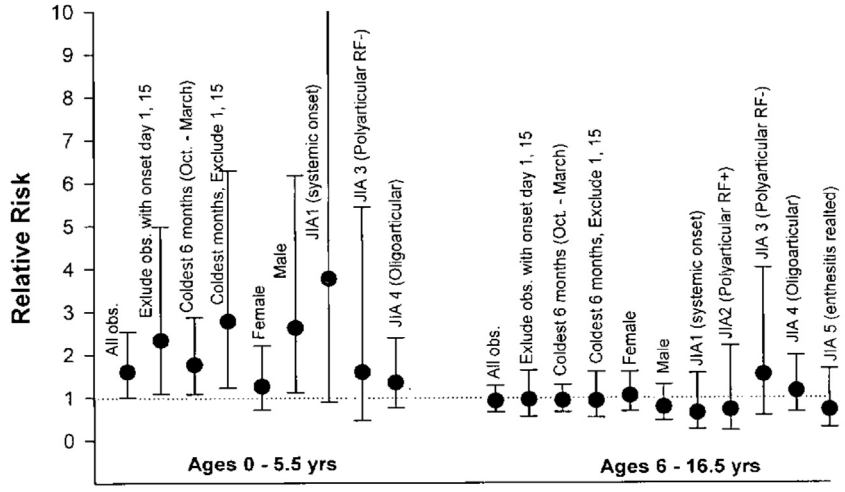

Fig. 1. Relative risks (and 95% CIs) of an onset event of JIA associated with a 10μg/m^3 of $PM_{2.5}$ for ages 0–5.5 and 6–16.5 and for selected subgroups.

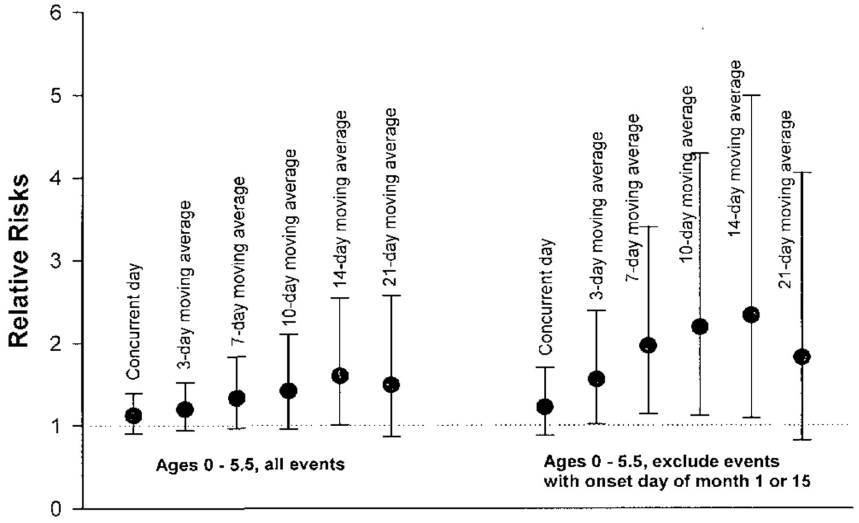

Fig. 2. Relative risks (and 95% CIs) of an onset event of JIA, 0–5.5 years of age, associated with a 10μg/m^3 of $PM_{2.5}$ for selected lagged average exposures, 1–21 days.

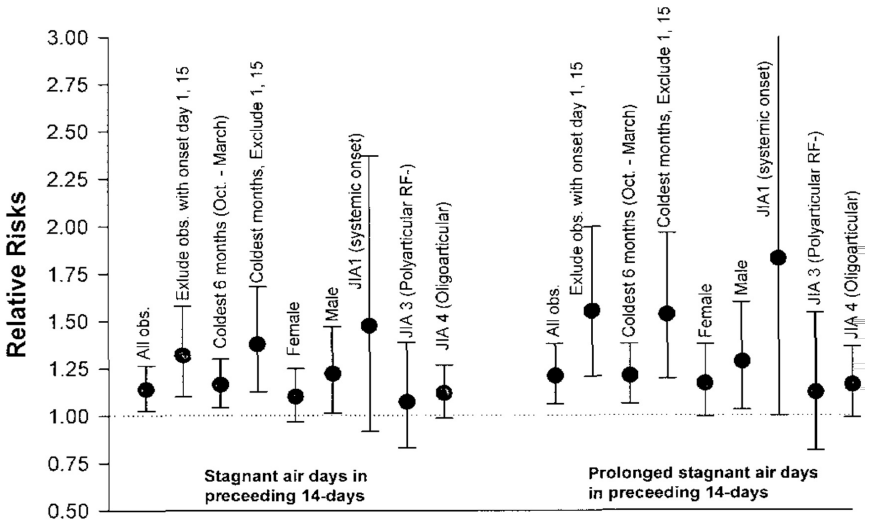

Fig. 3. Relative risks (and 95% CIs) of an onset event of JIA, 0–5.5 years of age, per one additional stagnant air day (Clearing index = 200) or one additional prolonged stagnant air day (stagnant air day immediately preceded by 2 additional stagnant air days) in preceding 14 days, for selected subgroups.

(RR=3.77, 95% CI 0.89–16.00). Also, for preschool aged children, much larger, but statistically insignificant, pollution-related excess risks were observed for boys versus girls.

Figure 1 contrasts the stratified relative risks across the various subgroups for preschool aged children (ages 0-5.5 yrs) versus older children (6–16.5 years). This figure further illustrates that, while elevated pollution concentrations are associated with elevated risk of JIA onset in the preschool aged children, no associations are observed for the older children. Regressions were run using various other age grouping, but the estimated pollution-related risk was strongest and most consistent with the age grouping 0–5.5 years of age.

Figure 2 presents relative risk estimates for different exposure windows. Although positive pollution-risk associations were observed for all of the exposure windows, the strongest and statistically significant associations were with approximately a 14-day lagged moving average (mean of the concurrent and previous 13 days).

The estimated pollution-related risk estimates were somewhat sensitive to the inclusion of weather variables in the conditional logistic regression models. When concurrent-day weather variables (including temperature, dew point temperature, and barometric pressure) were included as linear and quadratic terms, the estimated pollution-risk associations were slightly larger and statistically significant. When the 14-day lagged moving average of these variables were included, the pollution-risk associations were somewhat attenuated, but the weather variables were not statistically significant (p>0.15).

Models that replaced $PM_{2.5}$ with weather indicators of air stagnation further suggested that the risk of JIA onset is elevated during or following prolonged periods of air stagnation. For example, rather than use $PM_{2.5}$ concentration as the exposure variable, the number of "stagnant air days" or the number of "prolonged stagnant air days" in the preceding 14 days (including the concurrent day) was included in the conditional logistic regression model. "Stagnant air days" were defined as days when the

clearing index was ≤200. "Prolonged stagnant air days" were defined as stagnant air days immediately proceeded by 2 additional stagnant air days. The number of prolonged stagnant air days in previous 14 days is highly correlated with average $PM_{2.5}$ concentrations in those same days (*r*=approximately 0.84) and may be considered as a proxy variable for pollution exposure.

Figure 3 presents relative risk ratios (and 95% CIs) associated with one additional stagnant air day or one additional prolonged stagnant air day for preschool aged children. The risk of JIA onset was positively and significantly associated with the number of stagnant air days and even stronger associations were observed for the number of prolonged stagnant air days. The pattern of risk effects observed in Table III for stagnant air days is similar to the $PM_{2.5}$ effects presented in Figure 1 for preschool aged children. A significant association between risk of JIA onset and prolonged stagnant air days was observed for all preschool aged children (RR=1.21; 95% CI, 1.06–1.38; *p*=0.004). The association was even stronger when observations with onset day of month of 1 or 15 were excluded (RR=1.55; 95% CI, 1.21–2.00, *p*=0.001). When restricted to the 30 events during cold months that did not occur on the 1st or 15th, the prolonged air stagnation-related excess risk remained (RR=1.53; 95% CI, 1.20–1.97, *p*=0.001). Also, although there were only 16 events for systemic onset JIA, the prolonged air stagnation-related excess risk was relatively large and marginally statistically significant (RR=1.83; 95% CI, 1.00–3.34, *p*=0.050).

Discussion

To our knowledge, this is the first study to evaluate potential associations between JIA and ambient $PM_{2.5.}$ This study has several strengths. It uses the case-crossover design which controls for cross-subject differences that do not vary over time. It also controls by matching for weekday, month, time trends, and seasonality, which are essential when using exposure variables which are dependent on seasonal weather characteristics. Moreover, ambient exposures come from high quality pollution monitoring with correlated estimated exposure data due to the relative uniform temporal variability of particulate matter throughout the Wasatch Front. The study area has large day-to-day pollution variability making it a unique place from which to perform this type of regional ambient exposure assessment.

Furthermore, our cases come from a well-defined database in which cases have been carefully phenotyped and classified according to the ILAR criteria for JIA, which results in more homogenous subsets of JIA. Identifying associations within JIA subtypes is important because JIA is a complex, criterion-based disease, for which environmental factors, genes, and related immune responses may act differently in the different disease subsets and during different temporal phases of disease development. Gene-environmental interaction studies have found the strongest associations between smoking and CCP-positive RA in individuals harboring the susceptible HLA shared epitope (5, 29). In a similar manner particulate matter exposures may trigger specific immune reactions in certain JIA patients carrying specific genotypes.

While the finding of air pollution associations with JIA onset in preschool aged children is intriguing, this study has limitations and raises several important questions. First, there is a very sharp drop in the PM-onset association after 5.5 years of age. It is unclear to us why this would be the case. In Utah schools, 5.5 years is approximately the median age that children begin attending school. Once children are attending school, parents may become less attentive to onset times, giving school age children exposure measurement error in our model. Younger children may also be spending more time in the home exposed to indoor sources of fine particulate matter like tobacco smoke and cooking oil emissions. However, smoking rates in our region are low making the potential confounding effect of residential tobacco smoke less influential in our study. Acute infections or injuries are other potential triggers of inflammation which may be associated with JIA onset which we were not able to examine or control for in this study design. Interestingly, short term ambient $PM_{2.5}$ exposures have been shown to increase the risk of hospital admission for respiratory tract infection in adults but not in children (30-32).

The lack of precision of retrospective ascertainment of patient or parental reported JIA onset dates results in potential error in estimates of prior exposure. We acknowledge that the reported date is likely not a true proxy for onset of disease which is believed to be subclinical. However, the PM-onset associations are stronger when the estimated onset dates of the 1st and 15th of the month are excluded, which is consistent with the expectation of more robust PM-effect estimates with less exposure measurement error. In addition, the PM-onset associations are strongest in systemic onset JIA, the subtype of JIA with a clear onset date represented by high fever and systemic symptoms. Furthermore, the correct exposure window for a short term triggering effect on JIA onset is unclear. Empirically, an approximate 14-day lagged moving average of $PM_{2.5}$ is most strongly associated with the risk of reported JIA symptom onset. However, since JIA symptom onset dates other than in systemic JIA cases may not always be known with certainty, the distributed lag structure may reflect the fact that symptom onset is likely to follow an environmental trigger, and that increased risk is influenced by a short term cumulative exposure over a period of days or weeks.

It is also difficult to clearly separate the effects of air pollution and the effects of weather conditions that are associated with stagnant air conditions and relatively high air pollution. When the clearing index is low, indicating stagnant air conditions, there are elevated concentrations of primary and secondary pollutants from vehicles, industry, wood burning, and other local sources. Prolonged stagnant air conditions of several consecutive days can result in marked buildup of pollution levels. So while we assume that the effects seen are likely due to air pollution, they may be due to related conditions of stagnant air.

The effect estimates we have shown are relatively large compared to estimates of PM effects on cardiopulmonary deaths or ischemic heart disease (15, 33-36). Air pollution may have a larger effect on JIA disease presentation in young children compared with older school age children, and exposure to air pollution may increase the risk of JIA onset, especially in the preschool aged children. It has been shown that children with JIA who carry multiple HLA risk alleles develop their disease at younger ages (37). Thus, the higher prevalence of JIA in younger age groups may be related to environmental and genetic factors working together to trigger JIA onset.

In addition to the effects of short term inhaled $PM_{2.5}$ on systemic oxidative stress and inflammation (12), ambient $PM_{2.5}$ exposures have been shown to alter hemostasis (38-40) and a recent murine study of particulate matter exposure has examined alveolar macrophage IL-6 production and its effect on coagulation (41). The role of IL-6 in the particulate induced inflammatory and procoagulant response allows us to speculate whether the inflammatory stimulus in systemic JIA onset, an IL-6 mediated disorder with an underlying coagulation abnormality, is driven in our study by the IL-6 mediated effects of particulate exposures (42). Supporting this concept is a recent adult study identifying an immediate response of IL-6 levels to variations in particulate concentrations (43).

Potentially, younger children with heightened genetic susceptibility for JIA may be more affected by environmental triggers than older children with less genetic predisposition. How the environment acts to trigger variable temporal JIA onset in these susceptible populations remains unclear. Certainly, these results should be replicated in other study areas. Future studies are needed to examine the role of genetic susceptibility on the effect of short term pollution exposures with JIA symptom onset and disease presentation.

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