Kawasaki Disease and Exposure to Fine Particulate Air Pollution

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Objective To analyze associations of short-term exposure to fine particulate matter (diameter ≤ 2.5 μm [$PM_{2.5}$]), a measurable component of urban pollution, with the event date of fever onset for patients with Kawasaki disease (KD) residing in 7 metropolitan regions.

Study design A case-crossover study design was used. Time trends, seasonality, month, and weekday were controlled for by matching. We assembled $PM_{2.5}$ exposure measurements from urban monitors and imputed $PM_{2.5}$ to provide day-to-day temporal variability and resolution for time series indexes of exposures. Selected exposure windows (to 14 days) of $PM_{2.5}$ were examined.

Results A total of 3009 KD events were included for which the subject resided within a study metropolitan area and the event date occurred during years with available $PM_{2.5}$. The estimated ORs (with 95% CIs) of an event of KD associated with a 10 $\mu g/m^3$ $PM_{2.5}$ lagged moving average concentration of lagged exposure period (ie, concurrent, preceding day[s]) revealed no evidence of a consistent, statistically significant, positive association between elevated $PM_{2.5}$ exposure and increased risk of KD. Extended analysis with stratification by city, sex, age, ethnic origin, incomplete or complete clinical manifestations, the presence of coronary aneurysm, and intravenous immunoglobulin resistance did not provide evidence of a consistent, statistically significant, positive association between elevated exposure to $PM_{2.5}$ and increased risk of KD for any of the strata studied.

Conclusions This multicity study failed to establish a risk of the event of KD with short-term fine particulate exposure. Our negative findings add to the growing field of environmental epidemiology research of KD. *(J Pediatr 2016;177:179-83).*

Kawasaki disease (KD), a medium-vessel vasculitis characterized by fever and systemic features, is the most common form of acquired pediatric cardiac disease in the developed world.[1] The etiology of KD is believed to be multifactorial, with both genetic and environmental influences playing pathogenic roles.[2] Environmental influences associated with weather, spatial location, and temporal season have been shown to contribute.[3-9] Short-term environmental triggers contributing to the clinically recognized onset of KD remain unclear; however, regional climatology studies have suggested that a wind-transported antigen or toxin may trigger KD.[6-8] Rodo et al[7] proposed a shorter incubation period from exposure than is characteristic of an infectious organism requiring replication; rather, a paradigm was postulated whereby an idiosyncratic immune response, influenced by host genetics and triggered by exposure to an ambient environmental agent, results in the clinical syndrome known as acute KD.

Fine particulate matter (aerodynamic diameter ≤2.5-μm cutpoint [$PM_{2.5}$]) is a measurable component of ambient urban pollution. 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 inflammation-mediated disease, including coronary atherosclerosis and acute coronary events.[10,11] Numerous epidemiology studies have shown the effect of $PM_{2.5}$ on ischemic coronary artery events.[12,13] Children are particularly susceptible to inhalation exposures owing to more time spent outdoors, greater activity levels, and more air inhaled per body weight and lung surface area.[14] Positive associations of short-term ambient $PM_{2.5}$ exposure with flares of systemic proinflammatory responses have been identified in children.[15]

A complex pattern of immune cell activation, endothelial cell damage, and systemic inflammation, along with increased markers of oxidative stress, contribute to the pathogenesis of KD,[16] and the effects of short-term inhaled $PM_{2.5}$ on systemic oxidative stress and inflammation are evidenced in subjects exposed to

IVIG	Intravenous immunoglobulin
KD	Kawasaki disease
MSA	Metropolitan Statistical Area
$PM_{2.5}$	Aerodynamic diameter ≤2.5-μm cutpoint
PMSA	Primary Metropolitan Statistical Area

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short-term $PM_{2.5}$.[12,17] Furthermore, both a KD mouse model and a whole blood transcriptome analysis of acute and convalescent patients with KD provide evidence of activation of the innate immune system and the inflammasome.[18,19] It is known that fine particles of ambient pollution elicit inflammasome-mediated, toll-like, receptor-dependent innate immune responses.[20]

KD has an acute clinical onset, possibly triggered by an environmental exposure, such as ambient short-term $PM_{2.5}$. Previous studies lend credence to our hypothesis that the clinical presentation date of KD is associated with exposure to short-term pollution, specifically elevated $PM_{2.5}$.

Methods

This study was approved by the Institutional Review Boards of the participating institutions. Cases originated from physician-operated KD registries of patients diagnosed at the following pediatric specialty centers: The Hospital for Sick Children, Toronto; Boston Children's Hospital; Children's Memorial Hospital, Chicago; Rady Children's Hospital, San Diego; Primary Children's Medical Center, Salt Lake City; Children's Hospital Colorado, Denver; and Cleveland Clinic Children's Hospital. Cases were carefully phenotyped by board-certified pediatric physicians specializing in the care of children with KD. Subjects for the case-crossover study met the following inclusion criteria: (1) meeting the American Heart Association's diagnostic criteria for KD[21]; (2) date of fever onset during a period of $PM_{2.5}$ monitoring in the relevant metropolitan area; and (3) residence within a metropolitan area of study at the date of fever onset. The US metropolitan areas of study were classified as a Metropolitan Statistical Area (MSA) or a Primary Metropolitan Statistical Area (PMSA) as defined by the US Office of Management and Budget[22] and included the Salt Lake City–Ogden, Utah MSA; Denver, Colorado PMSA; Boston, Massachusetts–New Hampshire PMSA; San Diego, California MSA; Chicago, Illinois PMSA; and Cleveland–Lorain–Elyria, Ohio PMSA. The Toronto metropolitan area of study was the census metropolitan area of Toronto, Ontario as defined by Statistics Canada[23] plus the 3 communities of Whitby, Oshawa, and Burlington.

Pollution and Weather Data

For the 6 US cities, daily $PM_{2.5}$ data were collected from the US Environmental Protection Agency's Air Quality System.[24] For Toronto, $PM_{2.5}$ data were collected from the Ontario Ministry of the Environment.[25] For each city, data were collected from a central monitoring site, based on its central location within the metropolitan area and comprehensive collection of daily $PM_{2.5}$ data. We also collected $PM_{2.5}$ data from other available monitoring sites in the metropolitan areas. For each city, daily central-site $PM_{2.5}$ concentrations were regressed on $PM_{2.5}$ concentrations of other monitoring sites in the metropolitan area. $PM_{2.5}$ concentrations across sites were highly correlated (R^2 values ranging from 0.65 to 0.97). Missing daily $PM_{2.5}$ data at the central monitor were imputed using the regression results and the $PM_{2.5}$ concentrations at the nearest available $PM_{2.5}$ monitor. Except for Boston, there was very little missing data at the central site monitor (**Table I**; available at www.jpeds.com). Also, imputing missing data based on nearby monitoring sites resulted in exposure estimates with nearly identical mean and SD.

Weather data for all cities, including the temperature and dew point temperature data used in our statistical analyses, were collected from the National Climatic Data Center.[26]

Statistical Analyses

This analysis of KD cases was based on a case-crossover design, which is an adaptation of the retrospective case-control design. This approach matches exposures at the time of the event or shortly before the event with multiple periods when the event did not occur (control or referent periods) and evaluates for potential excess risk using conditional logistic regression. Details of this case-crossover design and approach, and the use of conditional logistic regression to estimate excess risks, are available elsewhere.[27,28] In brief, in this analysis, patients with KD served as their own controls, resulting in perfect matching on all participant-specific attributes that do not vary over time. Referent period exposures were matched on day of week in the same month and year as the onset of KD, resulting in either 3 or 4 control periods for each event date. For example, if the event day occurred on a Monday in a given month in a given year, then the referent days included the other 3 or 4 Mondays in that same month. By choosing matching referent periods that are the same day of the week and are close in time (the same month), this design also controls for time-dependent risk factors, such as day of week, seasonality, and long-term time trends.

We performed pooled analyses, for which observations for all cities were combined. Analyses stratified by individual city, as well as by sex and age, were conducted. We also performed analyses using only observations when 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 concurrent day temperature and dew point temperature (as both linear and quadratic terms).

$PM_{2.5}$ was included in the conditional logistic regression models as a continuous variable, and effect estimates are presented as ORs per incremental increases of 10 $\mu g/m^3$ $PM_{2.5}$. All statistical analyses were conducted using SAS version 9.4 (SAS Institute, Cary, North Carolina).

Results

The $PM_{2.5}$ air pollution data are summarized in **Table I**. The range in measured central site mean $PM_{2.5}$ levels among the metropolitan areas was 7.0-17.2 $\mu g/m^3$. As reported in **Table I**, daily $PM_{2.5}$ concentrations measured at the alternative monitors were highly correlated with those measured at the central site monitors (R^2 ranging from 0.65 to 0.97). The mean concentrations of $PM_{2.5}$ were nearly the same for observations only